Protocol *C2501001*

A PHASE 1, WITHIN COHORT, RANDOMIZED, DOUBLE BLIND, THIRD-PARTY OPEN, PLACEBO-CONTROLLED, SINGLE- AND MULTIPLE DOSE ESCALATION, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-06826647 IN HEALTHY SUBJECTS AND SUBJECTS WITH PLAQUE PSORIASIS

Statistical Analysis Plan (SAP)

Version: 1.0

Author: PPD PPD – Cambridge, MA 02139)

Date: 12-June-2018

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and Tyrosine kinase 2 (TYK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function (Murray PJ et al, 2007; O'Sullivan LA et al, 2007).

PF-06826647 is a potent TYK2 inhibitor with a good selectivity profile over other human kinases. Based on its cytokine inhibition profile, PF-06826647 is expected to target the T-helper 1 (Th1) and T-helper 17 (Th17) pathways, and Types I and II interferon signaling, directly by inhibiting TYK2, and to provide therapeutic benefit in the treatment of inflammatory conditions driven by Th1/Th17 and interferon immune responses.

This single- and multiple-ascending dose study is the first evaluation of PF-06826647 in humans. The goal is to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects and subjects with plaque psoriasis. The inclusion of a psoriasis cohort will facilitate optimal assessment of TYK2 modulation in vivo, given that Th1 and Th17 pathways are not up regulated in the absence of inflammation.

2.1. Study Design

The study may be conducted at 1-3 study sites in the United States.

This study is a Phase 1 combination, within cohort, randomized, double blind, third-party open, placebo-controlled, parallel group study with single- and multiple-dose escalation in healthy adult subjects, and multiple dosing in subjects with plaque psoriasis.

Subjects will be screened within 28 days prior to administration of study drug to confirm that they meet the subject selection criteria for the study, as described in Section 6.1 of the C2501001 clinical protocol. *A summary of the schedule of study participation and procedures for the single- and multiple ascending dose periods of the study are provided in their respective Schedule of Activities* in the protocol.

2.1.1. Healthy Subject Single and Multiple Ascending Dose Periods

*In the combined single ascending and multiple ascending dose (SAD/MAD) healthy subject cohorts (*except the Japanese cohort*) there will be approximately 8 subjects per dose level; 6 subjects will receive PF-06826647 and 2 subjects will receive placebo per the randomization code.* The health subject in Japanese cohort may include approximately 6 healthy subjects among which 4 subjects will receive PF-06826647 and 2 subjects will receive placebo.

Healthy subjects will be randomized (once) into the SAD period, at which time, they will receive treatment assignment (active PF-06826647 dose level or placebo) for both the SAD and MAD periods. Subjects will receive the same blinded treatment assignment (ie, active PF-06826647 or placebo) throughout in both the SAD (Period 1) and MAD (Period 2) periods.

During the single ascending dose (SAD) period, healthy subjects in Cohort 1 to Cohort 6 will receive single doses of 3, 10, 30, 100, 400, or 1600 mg of PF-06826647 or placebo in a dose escalation format as shown in the Study Schema (Figure 1) of the protocol. *The doses and meal condition of optional cohorts (Cohort 7 and Cohort 8) will be decided on emerging PK,* CCI *and safety data from prior SAD and MAD cohorts. Dose escalation to subsequent cohorts will be based on a minimum of 3 days of safety data and PK over 24 hours in a minimum of 6 subjects enrolled in a cohort. Subjects will reside in the clinical research unit (CRU) for the single ascending dose phase from Day -1 until completion of protocol assessments on Day 4. Dosing occurs on Day 1. Subjects will return to the unit on Day 8 (±1) day for the end of single dose period assessment and PK sample.*

At least 14 days (minimum wash-out period) will separate the beginning of the single and multiple dose periods (ie, at least 14 days will separate the single dose administered in the SAD and the first QD dose in the MAD); however, the minimum wash-out period may be adjusted based on emerging PK data. Based on the PK predictions and emerging PK data from this study, the currently planned starting dose in the MAD period is 30 mg (previously, a PF-06826647 starting dose of 10 mg was planned for the MAD period under the original protocol) is not expected to provide pharmacologically relevant exposure. In the multiple ascending dose (MAD) period, healthy subjects in Cohort 3 to Cohort 6 in Period 2 will receive doses of 30, 100, 400, or 1200 mg QD of PF-06826647 or placebo for 10 days (Day 1 through Day 10) with standard meal. The dose of Cohort 6 in MAD (Period 2) may be adjusted based on emerging data from earlier MAD cohorts in the trial. Subjects will be housed for the duration of the multiple dosing period, discharged on the morning of Day 14. Subjects will return for outpatient visits on morning of Day 17 for PK sample collection and Day 28 (±3 days) for end of study procedures. Based on emerging PK data, subject may be asked to return between Day 17 and Day 28 for an additional outpatient visit for PK sample collection. The additional PK sample will allow characterization of terminal half-lives at higher dose cohorts.

The multiple ascending dose study is planned to be initiated in the same subjects who previously participated in the single dose period at the same dose level, when possible (except for the optional twice daily, BID cohort and optional Japanese cohort). The highest dose to be tested in MAD will not exceed the highest dose tested in SAD cohort. Except the highest dose cohort, dosing in the MAD period will commence at the intended dose level (eg, 30 mg QD) if adequate single dose safety is demonstrated for next dose level (eg, 100 mg SAD). Subsequent MAD cohorts at higher dose levels (eg, 100 mg QD) will not be initiated until the single dose safety/tolerability has been established up to next dose level (eg, 400 mg), and a minimum of 10 days of safety and PK data from the preceding multiple dose cohort (eg, 10 mg QD) from at least 6 subjects (with at least one subject on placebo) has been reviewed. The remainder of the cohorts (except highest dose cohort) will follow a

similar escalation paradigm. Dosing in highest dose MAD cohort will commence if adequate safety is demonstrated in SAD cohort at the same or higher dose level and the projected exposure at steady state does not exceed NOAEL.

Twice daily (BID) dosing (for 10 days) may be evaluated as a separate cohort based on emerging PK data from this FIH study. Dosing in the BID cohort will not commence until review of safety data from the equivalent QD MAD cohort (minimum review of 10 day safety and PK data in at least 6 subjects, with at least one subject on placebo).

An optional Japanese cohort may also be included. If conducted, the dose administered will be equal to or less than the maximum PF-06826647 dose level administered in the healthy volunteer MAD period. Up to 8 subjects (including subjects on placebo) may be included in the optional Japanese cohort.

Administration of investigational product will be in fasted state in the SAD period and under standard meal conditions in MAD and in psoriasis cohorts. Based on the emerging PK, CCI [redacted] *and safety data, the meal condition requirement in SAD, MAD and psoriasis cohorts may be changed.*

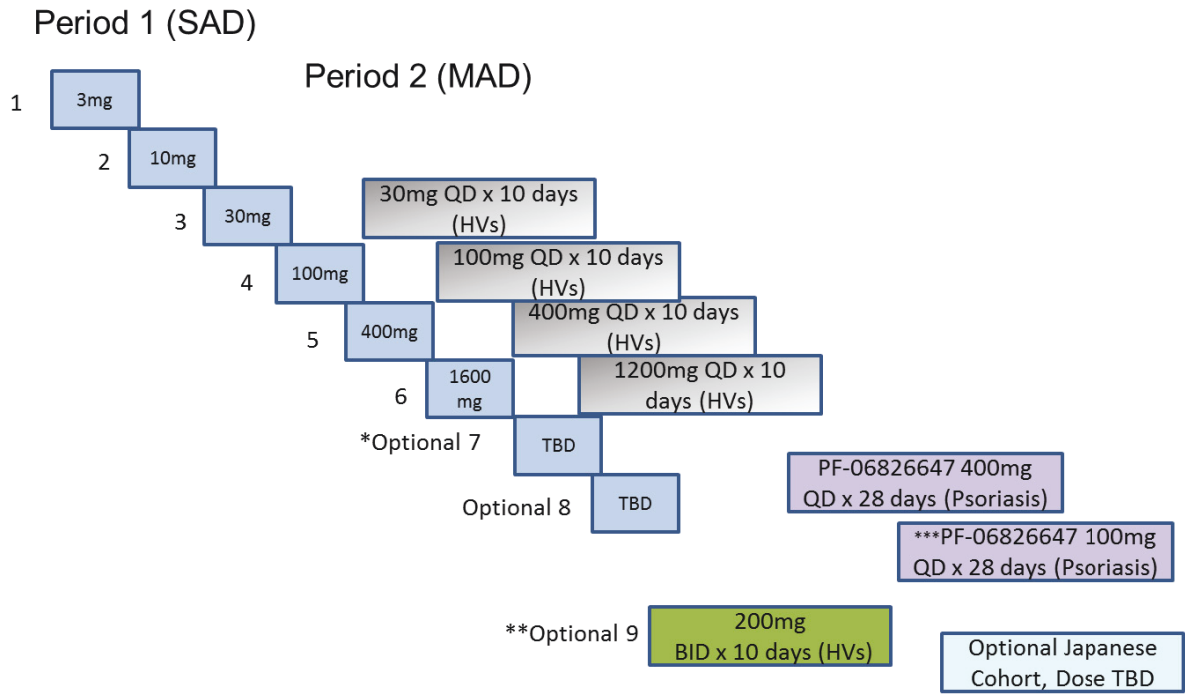
During the single and multiple ascending dose periods the dose increments and planned doses may be adjusted, as the study progresses dependent upon emerging PK, safety, and tolerability data. Other intermediate doses or lower doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for MAD cohorts if safety/tolerability issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. Any potential altered dose scheme will be equal to or less than a projected 3-fold increase in exposure from the previous highest dose if a higher dose is warranted to achieve exposure. The projected exposure will be equal to or less than a free AUC of 16600 ng.h/mL or free C_{max} of 1870 ng/mL following either single dose or multiple dose administration to ensure that the projected exposure of the altered planned dose scheme does not exceed the exposure limit.

2.1.2. Psoriasis Multiple Dose Cohorts

In the multiple dose psoriasis subject cohorts, approximately 42 subjects will be enrolled with approximately 14 subjects receiving placebo, and approximately 28 subjects receiving one of two possible PF-06826647 dose levels, for 28 days. PF-06826647 dose range for the psoriasis cohorts will be selected based on emerging PK, PD, and safety data from the healthy subjects SAD/MAD periods. Refer to Protocol Section 1.3.4.1 for psoriasis dose selection rationale. QD dosing is planned for psoriasis subjects, however, daily dosing regimen (eg, QD, BID) may be adjusted based on emerging PK data from the SAD/MAD periods. Psoriasis subjects who discontinue early from the trial may be replaced at the discretion of the sponsor. PF-06826647 dose level in psoriasis may be adjusted based on emerging clinical data from the planned interim analysis, at the discretion of the Sponsor. Any potential PF-06826647 dose adjustments for psoriasis Cohort 2 will be applied after review of PK, PD and safety data up to 28 day in the 400 mg psoriasis cohort.

Initiation of dosing in psoriasis subjects will be based on available safety data from the healthy subject MAD period. Psoriasis subjects enrolled into the multiple dosing period will receive PF-06826647 or placebo (QD) for 28 days, with a 56 day follow-up period post last dose. Doses will be selected based on emerging PK, PD and safety data from the study (not to exceed C_{max} and AUC_{0-24} limits of 1870 ng/mL and 16,600 ng·h/mL, respectively). Dosing in psoriasis subjects will commence if adequate safety is demonstrated in healthy subjects participating in the MAD period at the equivalent dose level. At a minimum, 10 day safety and PK data from at least 6 healthy subjects (with at least one subject on placebo) receiving the equivalent QD dose level will be reviewed to confirm that a given PF-06826647 dose is safe and well tolerated before administering PF-06826647 to psoriasis subjects. Subjects will be housed through Day 28 of the multiple dosing period, discharged on Day 28, to return for outpatient visits on the mornings of Days 35 (±3 days), 42 (±3 days), 56 (±3 days) and 84 (±3 days)(end of study). The 28 day treatment duration is supported by preclinical toxicology data and will facilitate assessment of CCI [redacted]*, as well as assessment of clinical endpoints (eg, PASI).*

Figure 1. Study Schema



Numbers 1 – 8 refer to subject cohorts. Subjects completing the SAD period will continue into the MAD period when applicable, after protocol defined washout and follow up.

** Cohorts 7 and 8 are optional single dose cohorts that may be conducted at discretion of Sponsor and based on emerging PK data. If conducted, the dose and meal condition will be decided based on emerging PK, PD, and safety data from the multiple ascending dose period of the trial.*

*** Cohort 9 is an optional cohort for assessment of twice daily (BID) PF-06826647 dosing. BID dose level will be determined based on emerging PK, PD, safety and tolerability data. The planned PF-06826647 dose level to be administered in the BID cohort is 200 mg twice daily (total daily dose of 400 mg).*

**** Based on interim analysis results from 400 mg psoriasis cohort, the PF-06826647 dose level for psoriasis Cohort 2 may be adjusted. The maximum dose administered to psoriasis subjects will not be expected to exceed the exposure at the maximum tolerated dose in the healthy subject MAD period.*

HVs = healthy volunteers

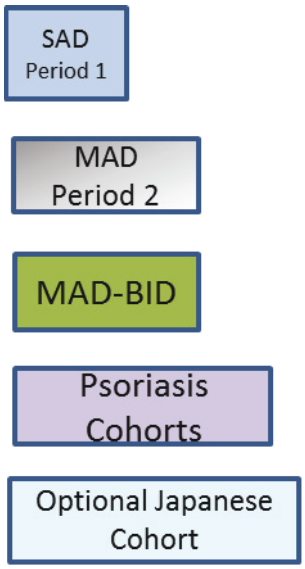
All cohorts are placebo controlled.

Note on optional Japanese subject cohort: if conducted, administration of PF-06826647 (or matching placebo) to Japanese subjects will occur once daily for 10 day duration, and subjects will follow the MAD period schedule of activities.

Figure 2. Legend for Figure 1

SAD = Single ascending dose Period 1 QD = once daily

MAD=multiple ascending dose Period 2 BID=twice daily



2.2. Study Objectives

2.2.1. Objectives: Healthy Subject Single and Multiple Ascending Dose Segments

2.2.1.1. Primary Objective

- *To determine the safety and tolerability of escalating single and multiple doses of PF-06826647 administered to healthy subjects.*

2.2.1.2. Secondary Objectives

- *To characterize the PK of PF 06826647 in plasma and urine (urine PK in multiple ascending dose period only) following oral administration of escalating single and multiple oral doses to healthy subjects.*

CCI

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

2.2.2. Objectives: Psoriasis Multiple Dose Segment

2.2.2.1. Primary Objective

- *To determine the safety and tolerability of multiple dose administration of PF-06826647 in psoriasis subjects.*

2.2.2.2. Secondary Objectives

- *To characterize the PK of PF-06826647 in plasma following oral administration of multiple oral doses to plaque psoriasis subjects.*
- *To evaluate the efficacy of PF-06826647 in moderate to severe plaque psoriasis.*

CCI

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

[redacted]

- [redacted]
- [redacted]

[redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Safety and pharmacokinetic (PK) data will be reviewed after each study cohort and period.

This is a third party open study, with the investigator and subject blinded to study treatment. Specific Pfizer personnel (analytical staff, medical monitor, clinician, statistician, and pharmacokineticist) will be unblinded to subject treatments in order to permit real-time interpretation of the safety and pharmacokinetic data, and to provide information necessary to potentially alter the dose escalation sequence. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/study staff until the conclusion of the study. Unblinding will not be performed until the final database has been locked for all cohorts. Final analysis will follow the official database release.

An interim analysis of the change from baseline at Day 28 in PASI score (psoriasis key secondary endpoint) will be conducted for the first psoriasis cohort (400 mg dose cohort). The analysis will be performed when approximately *21 psoriasis subjects from the 400 mg cohort complete through study Day 28. Outcomes from this interim analysis may inform dose selection decisions/adjustments for later psoriasis subject cohorts to be enrolled in the study. The interim analysis is not planned to impact the conduct of the initial 400 mg psoriasis cohort. The analysis is planned to be performed after dosing of the full 400 mg psoriasis cohort (n=21 subjects completing through study Day 28). Any decisions or dose adjustments that are taken, will be applied to the subsequent psoriasis cohort. A designated limited number of Sponsor colleagues will review the interim analysis results to support any dose related decisions. For the healthy SAD/MAD cohorts, this is a sponsor-open study, and the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or to support clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team*. A separate document containing the list of designated unblinded sponsor colleagues for the interim analysis will be prepared (see the Data Blinding Plan for further details) and saved in the SharePoint.

The psoriasis multiple dose cohorts are double-blind with respect to investigator and subject. The psoriasis multiple dose cohorts will be sponsor-open (unblinded interim analysis results will be reviewed by a designated limited number of sponsor colleagues). In addition to the planned interim analysis from the 400 mg psoriasis cohort, the sponsor may analyze selected clinical endpoints at the end of the Psoriasis treatment period (Day 28) before the follow-up period is completed for all cohorts. For the purpose of safety assessment, select individuals from sponsor may conduct unblinded reviews of individual subject safety data if needed to

ensure proper management of subject safety. If needed, a designated limited number of sponsor colleagues may conduct unblinded reviews of the data during the course of the study to facilitate PK/PD modeling.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No classical hypothesis testing will be performed.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Full Analysis Set

In general, the full analysis set is comprised of all randomized subjects. Analysis sets for PK, pharmacodynamic and safety data are defined in Sections 5.2, 5.3 and 5.4.

5.2. Pharmacokinetic Analysis Set

5.2.1. Concentration Analysis Set

The PK concentration population is defined as all enrolled subjects treated who have at least 1 concentration in at least 1 treatment period.

5.2.2. Parameter Analysis Set

The PK parameter analysis population is defined as all enrolled subjects treated who have at least 1 of the PK parameters of interest in at least 1 treatment period.

5.3. Pharmacodynamic Analysis Set

The pharmacodynamic analysis population is defined as all enrolled subjects who receive at least 1 dose of study medication and have at least 1 pharmacodynamic parameter in at least 1 treatment period.

5.4. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

5.5. Other Analysis Sets

None.

5.6. Treatment Misallocations

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

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

5.7. Protocol Deviations

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

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

5.7.1. Deviations Assessed Prior to Randomization

At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 – Section 4.4 of the protocol.

5.7.2. Deviations Assessed Post-Randomization

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

For the SAD/MAD and psoriasis cohorts, baseline is defined as the last pre-dose measurement from each period.

6.1. Endpoints: Healthy Subject Single and Multiple Ascending Dose Segments

6.1.1. Primary Endpoint(s) - Safety

- *Vital signs (blood pressure, pulse rate, oral temperature).*
- *Physical examination findings over time.*
- *12-lead ECG parameters.*
- *Incidence and severity of treatment emergent adverse events and withdrawals due to treatment emergent adverse events.*
- *Incidence and magnitude of treatment emergent clinical laboratory abnormalities including hematology (with differentials), fibrinogen, chemistry, fasting glucose, lipids, urinalysis.*
- *Change in 24 hour creatinine clearance from Day -1 and Day 10 (MAD only).*

6.1.2. Secondary Endpoint(s)

Systemic pharmacokinetics parameters (defined in Section 9.3.1 of the protocol) *will include:*

- *Single Dose: C_{max}, T_{max}, AUC_{inf}, AUC_{last}, AUC_{24}, $C_{max(dn)}$, $AUC_{inf(dn)}$, $AUC_{last(dn)}$, $t_{½}$, MRT, V_z/F, and CL/F (if data permit).*
- *Multiple Dose:*
- *Day 1: C_{max}, T_{max}, AUC_{tau} (tau=12 or 24 hours), $C_{max(dn)}$, $AUC_{tau(dn)}$.*
- *Day 10: C_{max}, T_{max}, AUC_{tau} (tau=12 or 24 hours), $C_{max(dn)}$, $AUC_{tau(dn)}$, $t_{½}$, C_{min}, C_{av}, R_{ac}, R_{ac},C_{max}, PTR, MRT, V_z/F,CL/F (if data permit).*
- *Urinary Pharmacokinetics (defined in Section 9.3.1 of the protocol; for healthy subjects, multiple ascending dose period only): Ae_{tau} and Ae_{tau}%, CL_r (if data permit).*

CCI [redacted]

6.2. Endpoints: Psoriasis Multiple Dose Cohorts

All subjects who receive at least one dose of randomized study medication, and have a baseline and at least one post-baseline measurement (after taking randomized study medication) will be included in the efficacy data analyses for the psoriasis cohorts.

6.2.1. Primary Endpoint(s) – Safety

- *Vital signs (blood pressure, pulse rate, and oral temperature).*
- *Physical examinations findings over time.*
- *12-lead ECG parameters.*
- *Incidence and severity of treatment emergent adverse events and withdrawals due to treatment emergent adverse events.*
- *Incidence and magnitude of treatment emergent clinical laboratory abnormalities including hematology (with differentials) chemistry, fasting glucose, lipids, urinalysis.*

6.2.2. Secondary Endpoints

- *Multiple Dose (defined in Section 9.3.1 of the protocol): C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn), $t_{½}$, PTR, C_{min}, C_{av}, MRT, V_z/F and CL/F (if data permit).*
- *Change from baseline in psoriasis area and severity index (PASI) score at Day 28.*

CCI [redacted]

[redacted]

6.3. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data,*
- *ECG results.*

6.3.1. Adverse Events

Any events occurring following start of the treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, washout or follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

6.3.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

6.3.3. Vital Signs

For subjects in study Periods 1 to 2, in each cohort, single supine measurements will be taken at times detailed in the Schedule of Activities given in the protocol.

The following vital signs endpoints will be determined:

- The maximum decrease and increase from baseline (pre-dose) over all measurements taken post-dose for supine systolic and diastolic blood pressures.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

6.3.4. ECG

12-lead ECGs will be recorded in triplicate for subjects in Periods 1 to 2 at times detailed in the Schedule of Activities given in the protocol.

A single 12-lead ECG will be obtained on all subjects at screening and follow-up as well as on selected visits as detailed in Schedule of Activities section of the Protocol.

The QT, QTc, PR, RR, QRS and heart rate will be recorded at each assessment time.

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

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

If not supplied, QTcB will be derived using Bazett's heart rate correction formula:

$$QTcB = QT / (RR)^{1/2} \qquad \text{where RR = 60/HR (if not provided)}$$

The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter. Baseline will be defined as the average of the triplicate predose recordings in each study period.

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

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

6.3.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

6.4. Pharmacokinetic Endpoints

Blood and urine samples for PK analysis of PF-06826647 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06826647 (if possible) from the plasma concentration-time data using standard noncompartmental methods*:*

	Parameter	***Definition***	***Method of Determination***
Plasma	*AUC_{last}*	*Concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})*	*Linear/Log trapezoidal method*
	$AUC\tau$	*Area under the plasma concentration-time profile over the dosing interval τ*	*Linear/Log trapezoidal method*
	AUC_{inf}[a]	*Area under the plasma concentration-time profile from time zero extrapolated to infinite time*	*AUC_{last} + (C_{last}*/k_{el}), where Clast* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis*
	C_{max}	*Maximum plasma concentration*	*Observed directly from data*

	Parameter	***Definition***	***Method of Determination***
	C_{min}	*Lowest concentration observed during dosing interval, τ; if measured at end of dosing interval, equivalent to* C_{trough}	*Observed directly from data*
	C_{av}	*Average concentration at steady state*	C_{av}*=* $AUC\tau,ss/\tau$
	T_{max}	*Time for* C_{max}	*Observed directly from data as time of first occurrence*
	$t_{1/2}$ [a]	*Terminal elimination half-life*	$Log_e(2)/k_{el}$, *where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression*
	CL/F[a]	*Apparent clearance*	*Dose/*AUC_{inf} *for SD* *Dose/*$AUC\tau$ *for MD*
	V_z/F[a]	*Apparent volume of distribution*	*Dose/(*AUC_{inf}*.* k_{el}*) for SD* *Dose/(*$AUC\tau$*.* k_{el}*) for MD*
	Rac	*Observed accumulation ratio based on AUC*	$AUC\tau$ *(ss)/*$AUC\tau$ *(sd)*
	$Rac,_{Cmax}$	*Observed accumulation ratio based on* C_{max}	C_{max} *(ss)/* C_{max} *(sd)*
	PTR	*Peak to Trough ratio*	C_{max}*,ss/*C_{min}*,ss*
	MRT	*Mean residence time*	$AUMC_{inf}/AUC_{inf}$, *where* $AUMC_{inf}$ *is the area under the first moment curve from time zero to infinity.*
	$C_{max}(dn)$	*Dose normalized* C_{max}	C_{max}*/Dose*
	$AUC_{last}(dn)$	*Dose normalized* AUC_{last}	AUC_{last}*/Dose*
	$AUC_{inf}(dn)$[a]	*Dose normalized* AUC_{inf}	AUC_{inf}*/Dose*
Urine	Ae_{τ}	*Cumulative amount of drug recovered unchanged in urine from 0 to dose interval (τ) hours post-dose*	*Sum of [urine concentration * sample volume] for each collection interval*
	$Ae_{\tau}\%$	*Percent of dose recovered unchanged in urine from 0 to dose interval (τ) hours post-dose*	$Ae\tau$*/Dose*100*
	CLr	*Renal clearance*	Ae_{τ}/AUC_{τ}

[a] *If data permit*

The PK parameters will be summarized descriptively by dose, regimen and study population (healthy subject and psoriasis subject) in accordance with Pfizer data standards. Summary statistics will also include the geometric mean and coefficient of variation for all parameters except T_{max}.

Dose normalized (to 1 mg) AUC and C_{max} *values of PF-06826647 will be plotted against dose (using a logarithmic scale if dose range is greater than 10-fold) for single- and multiple dose phases, and will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between the plasma PK parameters and dose. Additional PK analyses may be performed if deemed appropriate.*

Urine amounts of PF-06826647 and CLr will be listed and summarized descriptively, if data permits.

CCI *(fasted) will be used as Reference and AUC_{24} and C_{max} on Day 1 in MAD (QD) period (fed) as Test. Natural log transformed AUC_{24} and C_{max} will be analyzed using a mixed effect model with treatment (Dose levels) and period as a fixed effect and subjects within a treatment as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.*

CCI

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

7.1. Concentrations below the Limit of Quantification

In summary statistics for pharmacokinetic assayed values below the lower limit of quantification (LLOQ) will be set to zero. The imputations (eg, ½ LLOQ) may be considered in other analyses (eg, Pop-PK, PK/CC, and CCI), if deemed appropriate. In listings values below LLOQ will be reported as "<LLOQ" where LLOQ will be replaced with the numerical value for the lower limit of quantification. The LLOQ for various PK and CCI concentrations will be noted in all tables and listings.

7.2. Deviations, Missing Concentrations and Anomalous Values

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

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

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

7.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

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

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

While every effort has been made to pre-specify all analyses in this statistical analysis plan, should CCI [redacted], the analyses and the reasons for them may be detailed in the clinical study report. In all data presentations, results will be sorted by increasing dose level, starting with Placebo.

8.1. Sample Size Determination

8.1.1. Healthy Subject Single Ascending and Multiple Dose

A sample size of 8 subjects in each SAD and MAD cohort (with 6 active and 2 placebo) with approximately 48 subjects (assuming 6 cohorts) and 24 subjects for optional cohorts MAD BID cohort, Cohort 7 and 8 is not based on any statistical considerations. Sample size for optional Japanese subject cohort is not based on any statistical considerations, and may enroll up to 8 subjects in order to support characterization of the PF-06826647 PK profile in Japanese subjects. The sample size was based on the clinical consideration to provide safety and tolerability information and pharmacological considerations and on the need to minimize exposure to healthy subjects at each dose level. No formal inferential statistics will be applied to the safety, pharmacodynamic or pharmacokinetic data.

8.1.2. Psoriasis Multiple Dose

A sample size of approximately 42 subjects total is planned for the two psoriasis cohort(s). Psoriasis subjects will be randomized in each Psoriasis cohort to receive either active PF-06826647 (or placebo) with a planned randomization ratio of 2:1 (PF-06826647:Placebo) for each cohort. The between-subject standard deviation of absolute PASI change from baseline to Day 28 (obtained from Sponsor data on file) is assumed to be 8. The true difference between PF-06826647 and placebo is assumed to -7.8 (derived from the meta-analysis of the Tofacitinib data). Based on these assumptions the sample size is calculated to be 14 subjects per arm to provide approximately 80% power. This calculation assumes a one-sided alpha of 5%. The initial estimate of the total number of completers for the psoriasis cohort will be 42 with 21 (14 active +7 placebo) in each cohort. Based on the results from the planned interim analysis (described in Section9.7 of the protocol) PF-06826647 dose level or regimen may be adjusted for subsequent psoriasis subjects/cohorts enrolled after the interim analysis.

8.2. Statistical Methods

8.2.1. Statistical Method: Healthy Subject Single and Multiple Ascending Dose Segments

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

8.2.2. Statistical Method: Psoriasis Multiple Dose Segment

8.2.2.1. Method for Continuous Endpoints

The change from baseline in PASI scores at Day 28 in the psoriasis multiple dose segment is a secondary endpoint. The treatment effect for each of the test dose groups is the treatment difference in the mean change from baseline of PASI score at Day 28 between the test dose and the placebo. The estimates for treatment effect will be obtained by fitting a repeated measures linear model to the PASI change from baseline score. The model will include treatment (active doses and placebo), week and treatment-by-week interaction as fixed effects and baseline PASI score as a covariate. Estimates and 90% confidence intervals for treatment effect will be presented.

For all other continuous endpoints except gene expression and histology data longitudinal analyses will be performed using a mixed model repeated measures (MMRM) analysis. CCI Endpoints may be transformed prior to analysis as needed.

Each analysis will be performed with a restricted maximum likelihood (REML) MMRM analysis. Change scores from baseline to the last post treatment visit will be calculated and used as dependent variable. The model will include treatment and visit as fixed factors, along with the interaction of treatment and visit. Baseline measurement will be used as a covariate. An unstructured covariance structure will be used to model the within-subject variability. In the event there are difficulties with initially fitting an unstructured covariance matrix, a variety of methods will be used to facilitate the computations. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The model will be fit using SAS PROC MIXED. Least squares (LS) means of the treatment groups at each available visit along with 90% CIs will be presented. LS mean difference between treatment groups and between the current and baseline visit will be presented along with 90% confidence intervals. Least squares means and confidence intervals will be back transformed to an appropriate scale when necessary.

The sample SAS code for analysis of continuous data is presented in Section 9.2.

8.2.2.2. Method for Binary and Ordinal Endpoints

Binary and ordinal endpoints (such as CCI categories) will be summarized. For a binary endpoint, the sample size, percentage, and corresponding 90% confidence intervals for each treatment arm, difference of proportions, corresponding confidence intervals and 2-sided p-value will be presented.

The exact confidence interval of a binomial proportion will be computed due to Blyth-Still-Casella (Casella (1986)).[2] The estimated risk difference and the associated confidence interval of the risk differences will be computed based on the unconditional exact method proposed by Chan and Zhang (1999).[3]

The sample SAS code for analysis of binary data is presented in Section 9.2.

8.3. Statistical Analyses

8.3.1. Pharmacokinetic Analysis

8.3.1.1. Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06826647, the PK parameters detailed in Section 6.4 will be listed and summarized for subjects in the PK analysis set (as defined in Section 5.2). Missing values will be handled as detailed in Section 7. Each PK parameter will be summarized by dosing regimen and period, and will include the set of summary statistics as specified in the table below:

Table 1. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, $AUC_{last(dn)}$, $AUC_{inf(dn)}$, C_{min}, C_{av}, AUC_{τ}, $C_{max(dn)}$, R_{ac}, R_{ac},C_{max}, PTR, CL/F, and V_Z/F, Ae_{τ}, Ae_{τ}% and CL_r	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
MRT and $t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

There will be 1 summary table presenting all PK parameters. This will include data from all cohorts and will be paged by cohort. The treatment subheading will include the cohort number and dosing regimen information.

To assess the relationship between the PK parameters and dose, dose normalized AUC_{inf}, AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented and that data from both cohorts are presented on the plot.

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with dose as a fixed effect and subject as a random effect, for all cohorts in healthy volunteer; the similar exercise will be completed with patient cohort separately.

The purpose of these analyses is to obtain estimates of the intra-subject variation to assist in the planning of future studies. No treatment contrasts will be provided.

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

Presentations for PF-06826647 concentrations will include:

- a listing of all concentrations sorted by subject ID, cohort, dose and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

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

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

- Median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by meal condition and dose for Day 1 (0-24 h post dose) for Cohort 3, 4 and 5 (30, 100 and 400 mg cohorts).

- Boxplot of dose-normalized AUC_{24} and C_{max} on Day 1 in SAD and MAD separately by dose group and meal condition for Cohorts 3, 4 and 5.

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

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

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

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06826647 concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used. All statistical analyses related to the [redacted] will be performed as stated in Section 6.4.

[redacted]

8.4. Safety Analysis

For each of SAD/MAD (healthy volunteer cohort) and Psoriasis cohort a set of summary tables split by treatment will be produced separately to evaluate any potential risk associated with the safety and toleration of administering PF-06826647.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 6.2 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set.

8.4.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.4.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index and height. Each will be summarized by cohort and Overall in accordance with the sponsor reporting standards.

8.4.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.4.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

8.4.5. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards.

Mean change from baseline will be plotted against nominal time post dose. On each plot there will be one line for each treatment. The placebo data from all cohorts (for the SAD/MAD and Psoriasis cohorts) period will be plotted on the same figure using separate lines. Individual plots of changes from baseline will also be produced for each cohort and treatment.

8.4.6. Vital Signs Data

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by cohort, treatment and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.3.3.

Mean changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time post-dose. On each plot there will be separate line for each

treatment. Data from all cohorts will be plotted on the same figure using separate lines for different placebos. Corresponding individual plots of changes from baseline will also be produced for each cohort and treatment.

For supine systolic and diastolic blood pressure and pulse rate, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 90% confidence interval) and plotted (mean) for each cohort, dose and timepoint (including baseline).

Maximum absolute values and changes from baseline for vital signs (for supine) will also be summarized descriptively by treatment. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

8.4.7. ECG Data

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by cohort, treatment and time post-dose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.3.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time post-dose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure using separate lines for different placebos. Corresponding individual plots of changes from baseline will also be produced for each cohort and treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment. There will be 1 plot for each cohort.

Maximum increase from baseline for QTcF, heart rate, QT, PR and QRS will be summarized by cohort and treatment, according to sponsor reporting standards.

In addition for QTcF, heart rate and QT, the differences between each dose and placebo (dose – placebo) for each subject will be summarized and plotted (N, mean, 90% confidence interval) for each cohort, dose and timepoint (including baseline).

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by cohort and treatment using categories as defined in Section 9.4 (for QTc these correspond to ICH E14[1]). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single post-dose value ≥500 msec will also be produced for QTcF.

QTcB will be listed only and not summarized.

8.4.8. Other Safety Data

None.

8.4.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.4.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, serum or urine B-hCG for all females of childbearing potential, and urine or blood cotinine concentration will be obtained at Screening.

9. APPENDICES

9.1. Definition of Endpoints in Psoriasis Cohort

9.1.1. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index quantifies the severity of a subjects 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%.

Calculating PASI

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.

$PASI = 0.1Ah(Eh + Ih + Sh) + 0.2Au(Eu + Iu + Su) + 0.3At(Et + It + St) + 0.4Al(El + Il + Sl)$

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 response rate: At least 50/75/90% reduction in PASI relative to baseline PASI Score.

Linear-method Psoriasis Area and Severity Index (L-PASI)

A second method of calculating PASI will also be performed. A linear-scaling method will be applied to the Psoriasis Area and Severity Index calculation, adapting the classic calculation by using the actual percentage body surface area involved in psoriasis rather than categorizing the percentage involvement on a 7-point scale. The linear-scaling method will be calculated from the study database; investigator sites will only perform the classic PASI calculation during the study. The L-PASI score will be used for a sensitivity analysis.

L-PASI Calculation

L-PASI = 0.1(6xBh)x(Eh + Ih + Sh) + 0.2(6Bu)x(Eu + Iu + Su) + 0.3(6xBt)x(Et + It + St) + 0.4(6xBl)x(El + Il + Sl)

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

CCI

CCI

CCI

CCI

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

9.2. SAS Code

9.2.1. Continuous Data Analysis

Sample data set ds where for each subject and each visit the following information is stored in the row of the data set.

Id	Subject's id
Cbaseline	Change from baseline
visit	Visit of interest (stored as a categorical)
Trt	Treatment group (stored as a categorical)
Baseline	Baseline observation of the outcome

```
PROC MIXED DATA=<DATA>;
        CLASS    ID TRT VISIT;
        MODEL CBASELINE = TRT VISIT TRT*VISIT BASELINE /ALPHA=0.1
DFM=KR;
        REPEATED VISIT /SUBJECT= ID TYPE= UN;
        LSMEANS TRT*VISIT /ALPHA=0.1 CI PDIFF;
        ODS OUTPUT LSMEANS= LSM DIFFS=DIFF COVPARMS=COV;
RUN;
```

9.2.2. 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;
```

9.2.3. SAS Code for the Confidence Interval for Risk Difference using Chan and Zhang (1999)[3]

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

PD/EX ONE STD;

PO <POPULATION VARIABLE>;

OU <OUTCOME VARIABLE>;

RUN;

9.2.4. 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;

9.3. Assignment of Observations to the Visits

Visit window (applicable for efficacy and PRO endpoints) will be assigned to the subjects in the Psoriasis cohorts. The observations that are observed within the time window of (±3 days) around the target date will be assigned to the visit with the corresponding target date. The resulting assignment of observations to the post-baseline and baseline visits is shown in the following table.

Definition and Use of Visit Windows in Reporting

Visit Label	Targeted Day	Analysis Window
Screening	28 days prior to Day 1	1-30 days prior to Day 1
Baseline*	Day 1 (reference day)	Day 1 (reference day)
Week 1	Day 7	Days 4-10
Week 2	Day 14	Days 11-17
Week 3	Day 21	Days 18-24
Week 4	Day 28	Days 25-31
Week 5	Day 35	Days 32-38
Week 6	Day 42	Day 39-45
Week 8	Day 56	Day 53-59
Week 12	Day 84	Day 81-87

*In case Day 1 measurement is missing, the last available pre-dose will be considered as the baseline

If more than one observation from the same subject falls into the same window then the association of the observation with the visit will be done after the consultation with the study clinician and lead statistician.

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

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

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

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

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

10. REFERENCES

1. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

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

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