Protocol C4061001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE DOSE ESCALATION STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-07059013 AND OPEN-LABEL ASSESSMENT OF FOOD AND FORMULATION ON PHARMACOKINETICS OF PF-07059013 IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 1.2

Author: PPD (ECD Statistics)

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Version	Date	Author(s)	Summary of Changes/Comments
1.0	April 1, 2020	PPD	Original
1.1	September 28, 2020	PPD	1. Changes to reflect Protocol Amendment 1 from July 24, 2020 CCI [redacted] Section 6.6: Text added to reflect inclusion of additional biomarkers. Section 8.2.3: Added to describe additional analyses. 2. Add description of PVP use analyses Section 4: Specification of hypothesis and decision rules. Section 8.2.1: Analysis and data presentation specifications.
1.2	August 28, 2021	PPD	Section 2.1 Changes to crossover randomization schema for Part 3. Section 4.2 Added PVP analysis for Part 3. Section 6.2 Clarifiction of baseline measurements. Section 8.1 Clarification of study inference. Appendix 1 Categories for QTcF corrected to align with protocol. CCI [redacted]

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

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

This document is the original version from February 28, 2020.

2. INTRODUCTION

PF-07059013 is a novel small molecule allosteric modulator of hemoglobin that is currently being developed for the treatment of Sickle Cell Disease.

The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) of single and multiple ascending oral doses of PF-07059013 in healthy adult participants. Additionally, effects of different formulations and food on parameters, including PK, after single oral dose, may be explored. This study is the first time that PF-07059013 will be administered to humans, and the results obtained from this study will inform future clinical development of PF-07059013.

2.1. Study Design

This study consists of 3 parts, with ongoing review of safety, tolerability, PK and PD data planned.

Part 1 comprises of 4 periods with 2 interleaving cohorts of healthy adult participants. Part 1 Period 1 to 3 is investigator- and participant-blinded, sponsor-open, randomized, single ascending dose, with 3-period placebo substitution crossover, and Period 4 will be open-label.

Part 2 of this study will be investigator- and participant-blinded, sponsor-open, randomized, placebo-controlled, sequential, multiple ascending dose, with 3 planned cohorts of healthy adult participants. Two additional cohorts of healthy adult participants may be included to permit assessment of any of the following: repeat of a previously administered dose level; studying additional dose levels as dictated by the evaluated safety, tolerability or PK of earlier dose levels; or any other assessment needed to meet the objectives of this study.

Part 3 of this study will be an open label, randomized, 4-period crossover, single dose assessment of formulation and/or food effects in healthy adult participants.

Block randomization will be used to protect against possible temporal enrollment or dropout effects. In Part 1 with the 3-period crossover and no randomization for period 4, the block size of 3 (2:1 active to placebo ratio) will be used for each cohort (N=9). In Part 2 the block size of 4 (3:1 active to placebo ratio) will be used for each cohort (N=8). In Part 3 cohort (N=12) with the 4-period crossover, the block size of 4 will be used.

For all parts of the study, participants will be screened within 28 days of their first dose of investigational product. Participants will be admitted to the CRU on Day -1 and may be discharged at investigator discretion following completion of assessments per Schedule of Activities.

In Part 1 e*ach participant may receive up to 3 single oral doses of PF-07059013 suspension and up to 1 placebo dose. For Period 1 to 3, at each period, approximately 6 participants will receive a single dose of PF-07059013 suspension formulated with polymer, and approximately 3 participants will receive placebo formulated with polymer. In Period 4, a single dose of PF-07059013 suspension, formulated without polymer, will be administered at a dose level that has been previously administered in the same cohort. Between each dose administration to a given participant there will be a washout interval of at least 14 days.*

In Part 2 *each participant may receive multiple oral doses of PF-07059013 suspension (either with or without polymer, depending on results from Part 1) or placebo, over a duration of 14 days, depending on randomization.*

In Part 3 *each participant may receive single oral dose of suspension with different formulations, or tablet, either under fasted condition or following a high fat/high caloric meal. Between each dose administration to a given participant there will be a washout interval of at least 14 days.*

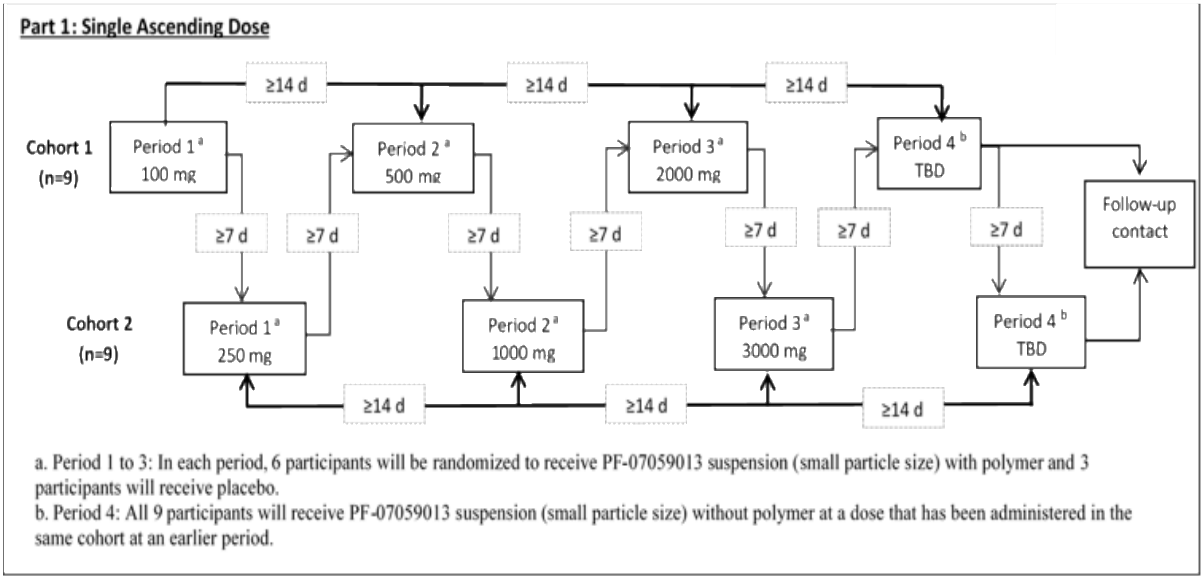
Participants who discontinue for non-safety related reasons prior to completion of the study may be replaced, at the discretion of the principal investigator (PI) and sponsor. The replacement participant(s) may or may not be required to complete all Periods of the cohort in which they are participating at the discretion of the PI and sponsor.

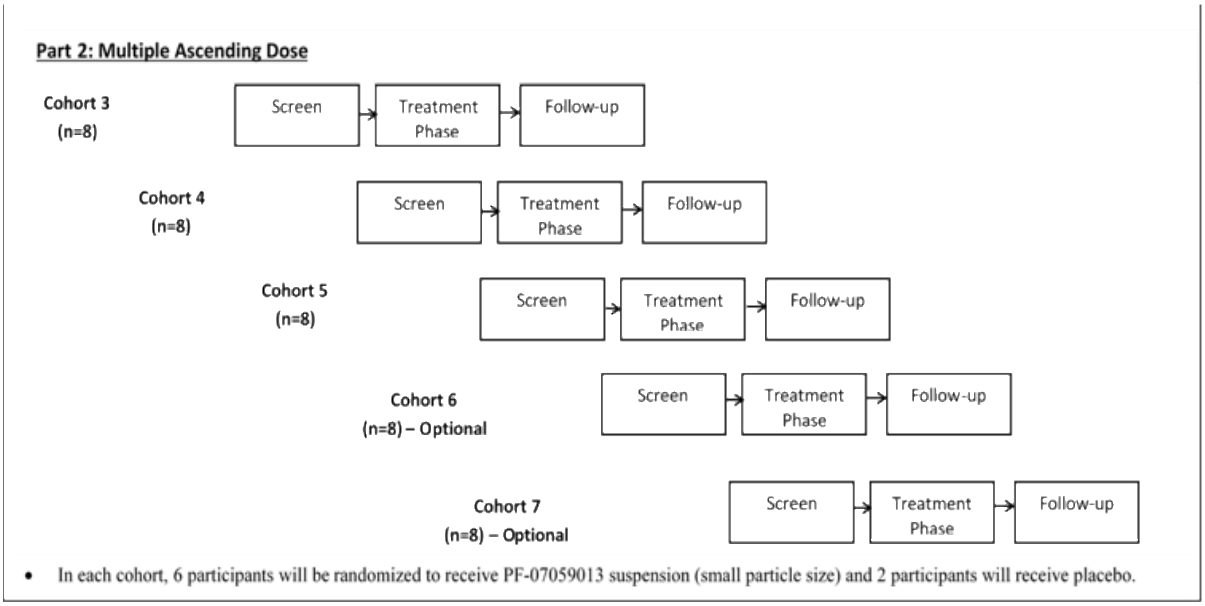
A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the Schedule of Activities and any requested unplanned visits.

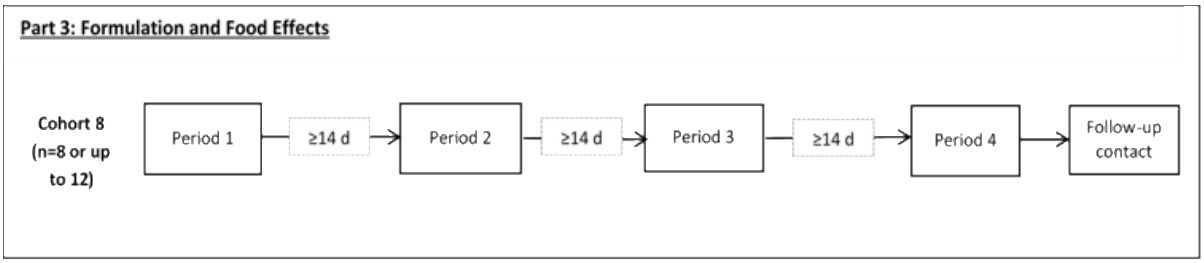
The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial.

A schematic of the overall study design is provided in Figure 1.

Figure 1. Sample Study Schematic







The table below presents the Part 3 randomization sequences.

Cohort	n	Period 1	Period 2	Period 3	Period 4
N=12	n=3	A	B	C	D
	n=3	A	B	D	C
	n=3	B	A	C	D
	n=3	B	A	D	C

Treatment A: PF-07059013 oral suspension (Small particle size), fasted, with Polyvinylpyrrolidone (PVP).
Treatment B: PF-07059013 oral tablet, fasted, without PVP.
Treatment C: PF-07059013 oral suspension (Small particle size), fed, with PVP.
Treatment D: PF-07059013 oral suspension (Moderate particle size), fasted, with PVP.

2.2. Study Objectives

2.2.1. Primary Objectives

In Part 1 and 2: *To evaluate safety and tolerability of single and multiple escalating oral doses of PF-07059013 suspension administered in healthy adult participants.*

2.2.2. Secondary Objectives

In Part 1 and 2: *To characterize the blood and plasma exposures of PF-07059013 following administration of single and multiple oral suspension doses in healthy adult participants.*

In Part 1 and 2: *To evaluate the PD profile of PF-07059013 following administration of single and multiple oral doses of suspension in healthy adult participants.*

CCI [redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. Safety, pharmacokinetic (PK) and pharmacodynamic (PD) data will be reviewed after each cohort.

This is a sponsor open study, with the investigators and participants blinded to study treatment (with exception of Part 1 period 4 and Part 3). Specific Pfizer personnel (e.g.

analytical staff, medical monitor, clinician, statistician, and clinical pharmacologist) will be unblinded to subject treatments in order to permit real-time interpretation of the safety and PK/PD 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.

4. HYPOTHESES AND DECISION RULES

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

- CCI [redacted]

[redacted]

5. ANALYSIS SETS

5.1 Full Analysis Set

Not applicable. Analysis sets for PK, PD, safety [redacted] data are defined in Sections 5.2, 5.3, 5.4 and 5.5.

5.2 Pharmacokinetic Analysis Set

5.2.1 Concentration Analysis Set

The PK concentration population will be defined as all randomized participants who received at least 1 dose of PF-07059013 and in whom at least 1 plasma and blood concentration value is reported.

5.2.2 Parameter Analysis Set

The PK parameter analysis population will be defined as all randomized participants who received at least 1 dose of PF-07059013 and who have at least 1 of the PK parameters of interest calculated.

5.3 Pharmacodynamic Analysis Set

The PD analysis population is defined as all randomized participants who received at least one dose and have at least one PD assessment in at least one cohort.

5.4 Safety Analysis Set

All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

[redacted]

5.6 Treatment Misallocations

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

If a participant takes a treatment that is not consistent with the treatment they are randomized to then they will be reported under the treatment that they actually receive for all safety, PK [redacted], where applicable.

5.7 Protocol Deviations

Participants who experience events that may affect their PK/PD profile (eg dosing error, etc) may be excluded from the PK/PD 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 participants against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 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

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

In this section, the safety endpoints that will be measured during the study are detailed. Where applicable, details of the endpoints to be derived and definition of baseline are also provided.

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

- adverse events,
- clinical laboratory data,
- vital signs data,
- ECG and telemetry results.

6.2.1. Adverse Events

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

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

6.2.2. 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 participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be defined as the measurement on Day -1 of each period of Part 1 and Part 3, and treatment phase of Part 2, or the last available corresponding pre-dose collection time point including unplanned measurements (whichever occurs later).

6.2.3. Vital Signs

Single supine blood pressure, pulse rate, oral temperature and respiratory rate measurements will be taken at times detailed in the Schedule of Activities given in the protocol.

Baseline will be defined as pre-dose measurement on Day 1 of each period of Part 1 and Part 3, and treatment phase of Part 2 or the last available corresponding pre-dose collection time point including unplanned measurements (whichever occurs later).

The following vital signs endpoints will be determined:

- Actual value of supine (and orthostatic if measured) systolic and diastolic blood pressure, pulse rate, oral temperature and respiratory rate at each time point.

- Change from baseline in supine (and orthostatic if measured) systolic and diastolic blood pressure, pulse rate, oral temperature and respiratory rate at each time point.

- The maximum decrease and increase from baseline over all measurements taken post-dose for supine systolic and diastolic blood pressures, pulse rate, oral temperature and respiratory rate.

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.

6.2.4. ECG and Telemetry

ECG

A single 12-lead ECG will be obtained on all subjects at screening.

Triplicate 12-lead ECGs will be recorded on all subjects at all other time points as detailed in the Schedule of Activities given in the protocol.

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

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

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

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 pre-dose recordings collected on Day 1 of each period of Part 1 and Part 3, and treatment phase of Part 2.

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

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will also be calculated.

Telemetry

To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1 of Part 1, and subsequently collected for 12 hours after the dosing.

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythm of potential clinical concerns, which will document the time, duration and description of the clinically significant event.

6.2.5. 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.

6.3. Pharmacokinetic Endpoints

Blood samples for PK analysis of PF-07059013 will be taken according to the Schedule of Activities given in the protocol. The following PK parameters will be calculated for PF-

07059013 (if possible) for Part 1 and Part 3 (Table 1), and Part 2 (Table 2, Table 3) from the concentration-time values using standard non-compartmental methods.

Table 1. Plasma and Blood PK Parameters for Part 1 and Part 3 (Single Dose)

Parameter	Definition	Method of Determination
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted]

Table 2. Plasma and Blood PK Parameters for Part 2 (Multiple Doses)

Parameter	Day	Definition	Method of Determination
AUC_τ	1, 7, 14	Area under the plasma concentration-time profile from time zero to time τ (tau), the dosing interval, where τ = 24 hours for QD dosing.	Linear/Log trapezoidal method
C_{max}	1, 7, 14	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 7, 14	Time for C_{max}	Observed directly from data as time of first occurrence
CCI	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]
C CI	[redacted]	[redacted]	[redacted]
C CI	[redacted]	[redacted]	[redacted]
CC I	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]
CCI	[redacted]	[redacted]	[redacted]

CCI [redacted]

CCI

6.4. PD Endpoints

Change from baseline and percent change from baseline will be calculated for all biomarkers. Baseline will be defined as the pre-dose value collected on Day 1. Blood samples will be collected for measurement of p20 and p50 as specified in the SoA.

CCI

CCI

6.6.1. Immunogenicity

Immunogenicity will not be assessed in this study.

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

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 dosing error), 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

CCI [redacted]

[redacted]

8.2. Statistical Analyses

8.2.1. Pharmacokinetic Analysis

To assess the pharmacokinetics of PF-07059013, the PK parameters detailed in Section 6.3 will be listed and summarized for subjects in the PK parameter analysis set (as defined in Section 5.2.2). Missing values will be handled as detailed in Section 7. Each PK parameter will be summarized for each Part by dose, treatment group (where applicable) and day (where applicable). Summary will include the set of summary statistics as specified in Table 4 for the single dose and Table 5 for the repeat-dosing, respectively.

Table 4. PK Parameters to be Summarized Descriptively for Part 1 and Part 3 (Single Dose)

Parameter*	Summary Statistics
CCI C_{max}, CCI CCI	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
C C I	CCI

*dose normalized parameters are only applicable to Part 1

Table 5. PK Parameters to be Summarized Descriptively for Part 2 (Multiple Doses)

Parameter	Summary Statistics
CCI C_{max}, CCI CCI	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
C C I	

There will be 1 summary table for each part of the study presenting all PK parameters. The treatment subheading will include the cohort number and dose information.

For Part 1, dose normalized (to 1 mg) CCI C_{max} will be plotted against dose (using a log scale) and will include individual subject values and the geometric means for each

dose. For Part 2, dose normalized (to 1 mg) CCI [redacted] C_{max} will be plotted against dose (using a log scale) for each Day (1, 7 and 14), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. A footnote will be added to the plots to indicate that geometric means are presented. The main analyses of Part 1, Part 2 and Part 3 data are descriptive in nature.

Presentations for blood and plasma PF-07059013 concentrations will include:

- A listing of all concentrations sorted by study Part, treatment, subject ID, and nominal time post-dose. The concentration listing will also include the actual collection times.
- Median concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by dose and cohort (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).
- Mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose, cohort and time post-dose).
- Individual concentration time plots by dose (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale) for each study treatment separately.

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-07059013 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.

Urine PF-07059013 PK (Part 2 only) concentration and sample collection volumes will be listed by cohort, dose and subject. The urine PK parameters listed below in Table 6 will be summarized descriptively.

CCI [redacted]

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

The comparison of formulation of PF-07059013 with and without PVP will be performed according to the Pfizer's Clinical Pharmacology Guidance Chapter 5 for analysis of absolute and relative bioavailability studies using repeated measures ANOVA on natural log-transformed blood CCI [redacted] for the two dose levels separately. The results of analyses will be presented in tabular format including model estimates of geometric means for each group, adjusted geometric means ratios (Test/Reference) and 80% confidence interval for the ratios.

CCI [redacted].

8.2.2. Pharmacodynamic Analysis

The analysis time windows are specified in SOA for each Part of the study. The analysis population is the Pharmacodynamic Analysis Set (defined in Section 5.3) Descriptive statistics will be used to summarize the data for each Part of the study separately.

Presentations for pharmacodynamic endpoints will include:

- A listing of all pharmacodynamic values sorted by treatment, subject ID, study day (for Part 2) and nominal time post-dose. The pharmacodynamic endpoint listing will also include the actual collection times.
- A summary of all pharmacodynamic values and their changes from baseline by treatment,study day (for Part 2) and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), and minimum, maximum.
- Mean/median value and change from baseline over time plots (on linear scale) by treatment and study day (for Part 2 i.e. Day 1, 7 and 14).

CCI [redacted]

8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-07059013.

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 (as defined in Section 5.4).

Descriptive statistics will be used to summarize the data for each Part of the study separately.

Presentations for safety endpoints will include:

- A listing of safety endpoints sorted by treatment, subject ID, and study day post first dose of the current treatment period.
- A summary by treatment group including the number of subjects at risk, numbers and percentages of subjects meeting the categorical criteria.

8.3.1. 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 group and the study Part separately.

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

8.3.2. Demographic Data

A break down of demographic data will be provided for age, race, ethnicity, weight, body mass index and height. Each will be summarized by treatment and study Part in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

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

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

8.3.4. Adverse Events

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

8.3.5. Laboratory Data

Laboratory data will be listed and summarized by treatment and study Part in accordance with the sponsor reporting standards. Baseline is as defined in Section 6.2.2.

8.3.6. Vital Signs Data

Absolute values and changes from baseline in supine systolic and diastolic blood pressure, oral temperature, pulse rate and respiratory rate will be summarized by treatment and reported separately by Study Part in accordance with the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, oral temperature, pulse rate and respiratory rate for each treatment will be plotted against time post-dose, and by study day for Part 2 i.e. Day 1, 7 and 14, for each Study Part separately. On each plot there will be 1 line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum and minimum values and changes from baseline for vital signs will also be summarized descriptively by treatment, for each study Part separately, using categories as defined in Appendix 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.

8.3.7. ECG and Telemetry Data

ECG

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment, which will be reported for each study Part separately in accordance with the sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time post-dose, and by study day for Part 2 i.e. Day 1, 7 and 14, and separately reported for each study part. On each plot there will be 1 line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each 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 a separate plot for each study Part.

Maximum increase from baseline for QTcF, heart rate, QT, PR and QRS will be summarized by treatment, separately for each study Part in accordance with the sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment, for each study Part separately, using categories as defined in Appendix 1 (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.

Telemetry

Telemetry data will be listed for those subjects with abnormal rhythms, showing the treatment, time, duration and description of the clinically significant event.

8.3.8. Other Safety Data

Not applicable.

8.3.9. Concomitant Treatments

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

8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s) and follicle-stimulating hormone (FSH) concentrations for all females of childbearing potential and urine drug screen will be obtained at Screening.

These data will not be brought in-house, and therefore will not be listed.

Any other screening data that is captured in the study database will be listed.

CCI [redacted]

[redacted]

CCI [redacted]

9. REFERENCES

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

Appendix 1. 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

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

CCI