Protocol C1061010

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF PF-06835919 IN HEALTHY ADULT JAPANESE PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: **1**

Date: 18MAR2020

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C1061010 is based on the protocol dated 4MAR2020.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 18 MAR 2020	Original 04Mar2020	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1061010. 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

As this is an inpatient, healthy volunteer study estimands are not applicable. The below table is copied directly from the protocol.

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of PF-06835919 following multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• Assessment of AEs, clinical laboratory tests, vital signs (including BP and PR) and 12-lead ECG.
• To evaluate the PK of PF-06835919 following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• PK parameters[a] for PF-06835919: Day 1 and Day 7: C_{max}, T_{max}, AUC_{tau} Day 7: $t_{½}$, as data permit.
Exploratory:	**Exploratory:**
• To evaluate the PK parameters of PF-06835919 CCI [redacted] following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• PK parameters[a] for PF-06835919: Day 1 and Day 7: dose normalized C_{max} and AUC_{tau} Day 7: C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F, as data permit. • CCI [redacted]

a. For complete definition of all PK parameters refer to Table 2.

2.2. Study Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics (PK) of multiple oral doses of PF-06835919 300 mg QD in healthy adult Japanese participants.

A total of approximately 8 healthy participants will be enrolled in this study. Participants will be randomized to 2 groups to receive PF-06835919 or placebo treatment with a randomization ratio of 3:1. The overall study design is summarized below in Table 11.

Table 1. Study Design and Treatments

Group	Number of Participants	Treatments[a] (7 Days)
1	6	PF-06835919 300 mg QD
2	2	Placebo QD

a. Study treatment as 3 x 100 mg PF-06835919 or matching Placebo tablets

All participants will provide informed consent and undergo screening evaluation to determine their eligibility. Participants will be screened within 28 days of the first dose of study intervention. Eligible participants will be admitted to the Clinical Research Unit (CRU) on Day -1 and will be required to remain in the CRU until morning of Day 10 for a total of 10 overnight days. After PK sampling at 72 hours post last dosing, all participants will be discharged from the CRU following completion of the discharge evaluation, which includes adverse event (AE) monitoring, physical examination, vital signs, electrocardiogram (ECG) measurements, and safety laboratory tests. Participants will receive a Follow-up telephone contact 28-35 days after the last dose on Day 7. The total duration of participation for each participant, including screening and Follow-up telephone contact, will be approximately 7 to 10 weeks.

Participants discontinuing prior to the completion of the study may, at the discretion of the investigator and sponsor and for reasons other than safety, be replaced by another participant who will repeat the treatment of the participant being replaced.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints include safety and PK of PF-06835919 whose details are provided below.

Safety:

The standard safety endpoints include adverse events (AEs), clinical laboratory tests, vital signs (including blood pressure and pulse rate), and 12-lead ECG. These will be further described in section 3.4.

PK:

The following plasma PK parameters for PF-06835919 will be derived using the actual PK sampling times. In the case that actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

- Day 1 and Day 7: C_{max}, T_{max}, AUC_{tau}
- Day 7: $t_{½}$ as data permit

Definition and additional details of the PK parameters are provided below in Table 2.

3.2. Other/Exploratory Endpoint(s)

The exploratory endpoints include the following PK parameters for PF-06835919:

- Day 1 and Day 7: dose normalized C_{max} and AUC_{tau}
- Day 7: C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F, as data permit.

CCI [redacted]

[redacted]

[redacted]

Definition and additional details of the PK parameters are provided below in Table 2.

Table 2. Definition of Plasma PK Parameters for PF-06835919 CCI [redacted]

Parameter	Day(s)	Definition	Method of Determination
AUC_{tau}	1, 7	Area under the plasma concentration time profile from time zero to time tau (τ), the dosing interval, where τ = 24 hours for QD dosing.	Linear/Log trapezoidal method
C_{max}	1, 7	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 7	Time for C_{max}	Observed directly from data as time of first occurrence
C_{min}	7	Minimum plasma concentration during the dosing interval	Observed directly from data
R_{ac}	7	Observed accumulation ratio	Day 7 AUC_{tau}/Day 1 AUC_{tau}
$R_{ac,Cmax}$	7	Observed accumulation ratio for C_{max}	Day 7 C_{max}/Day 1 C_{max}
PTR	7	Peak to trough ratio	C_{max}/C_{min}

$t_{½}$[a]	7	Terminal half life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
CL/F[a,b]	7	Apparent clearance	$Dose/AUC_{tau}$
V_z/F[a,b]	7	Apparent volume of distribution	$Dose/(AUC_{tau} * k_{el})$
AUC_{tau} (dn)[b]	1, 7	Dose normalized AUC_{tau}	$AUC_{tau}/Dose$
C_{max}(dn)[b]	1, 7	Dose normalized C_{max}	$C_{max}/Dose$
CCI [redacted]	[redacted]	[redacted]	[redacted]

a. As data permit.
b. To be calculated for PF-06835919 only.
C [redacted]
C

Any potential exploratory analysis of banked biospecimens may not be reported in this study.

3.3. Baseline Variables

Baseline variables are those collected on Day 1 prior to dosing or before Day 1. The demographic data of age, race, weight, body mass index, and height will be summarized by treatment in accordance with the sponsor reporting standards.

3.4. Safety Endpoints

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

- AEs,
- Clinical laboratory tests,
- vital signs data,
- ECG results.

3.4.1. Adverse Events

Any events occurring following start of treatment (either PF-06835919 or placebo) will be counted as treatment emergent. Events that occur in a non-treatment period (i.e. follow-up) within the lag time of 28 days will be counted as treatment emergent and attributed to the previous treatment taken. Similarly, the time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.4.2. Laboratory Data

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

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into

account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last predose measurement collected on Day -1 prior to Day 1 randomization and dosing. Results from only the planned study visits will be considered for baseline assessment.

3.4.3. Vital Signs

Single supine blood pressure and pulse measurements will be taken at all time points listed in the Schedule of Activities given in the protocol. Baseline will be defined as the measurement obtained on Day 1 0H predose.

The maximum decrease and increase from baseline over all measurements taken postdose for supine systolic and diastolic blood pressures will be determined. The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the entire study 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.

3.4.4. ECG

Single supine 12-lead ECG will be taken at all time points listed in the Schedule of Activities given in the protocol. Baseline will be defined as the measurement obtained on Day 1 0H predose.

The QT, QTcF, PR, 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:

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

The maximum absolute value (postdose) and the maximum increase from baseline 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 postdose measurement to give the change from baseline. The maximum of these values over the entire study 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.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database. For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Evaluable	All participants randomly assigned to and receiving at least 1 dose of study intervention
PK Concentration	The PK concentration population is defined as all participants who receive at least 1 dose of PF-06835919 and who have at least 1 measurable concentration of PF-06835919 [redacted]
PK Parameter	The PK parameter population is defined as all participants who receive at least 1 dose of PF-06835919 and who have at least 1 of the PK parameters of interest calculated.
Safety	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.

5. GENERAL METHODOLOGY AND CONVENTIONS

This is a double-blind and sponsor-open study. Specific Pfizer personnel (analytical staff, medical monitor, clinical leads, clinicians, statistician, programmers, data managers and pharmacokineticists and people shadowing these team members) will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data. Treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/site staff until the conclusion of the study. Final analysis will follow the official database release.

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses or decision rules.

5.2. General Methods

Descriptive statistics, including the sample size, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. Some measures will be summarized using graphical representations by treatment and visit, where appropriate.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data:

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

5.3.2. Pharmacokinetics Data:

Methods to handle missing PK data are described below.

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.)

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 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.

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 from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

The analyses of primary endpoints for safety will be described in the Section 6.4.

PK Endpoint (s)

To assess the pharmacokinetics of PF-06835919, the PK parameters detailed in Section 3.1 will be listed, summarized and plotted by PK sampling days for subjects in the PK parameter set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.2. Each plasma parameter will be summarized by day and will include the set of summary statistics as specified in the table below:

Table 3. Plasma PK Parameters for PF-06835919 to be Summarized Descriptively

	Parameter	Summary Statistics
Primary	AUC_{tau}, C_{max},	N, arithmetic mean, median, CV%, standard deviation (STD), minimum (min), maximum (max), geometric mean and geometric CV%
Primary	T_{max}	N, median, min, max.
Primary	$t_{½}$[a]	N, arithmetic mean, median, CV%, STD, min, max.
Exploratory	AUC_{tau}(dn), C_{max}(dn), CL/F[a], V_Z/F[a], C_{min}, PTR, R_{ac} and $R_{ac,Cmax}$	N, arithmetic mean, median, CV%, STD, min, max, geometric mean and geometric CV%

a. if data permit

There will be one summary table presenting all primary PK parameters. This will be paged by day as appropriate. Exploratory endpoints will be presented in a separate table.

6.2. Exploratory Endpoint(s)

CCI [redacted]

[redacted]

[redacted]

a. if data permit

CCI [redacted]

Median plots of the pre-dose concentrations against day for PF-06835919 CCI [redacted] will be provided separately in order to assess the attainment of steady-state.

The following supporting data from the estimation of $t_{½}$ on Day 7 for PF-06835919 CCI [redacted] will be listed and analyzed: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); and the first, last, and number of time points used in the estimation of k_{el}.

Presentations for PF-06835919 CCI [redacted] plasma concentrations will include:

- a listing of all concentrations sorted by subject ID, day 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 day and nominal time post dose, where the set of statistics will include n, mean, median, STD, CV, min, max 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 day (Days 1 and 7 plotted on the same graph) based on the summary of concentrations by day and time post dose.
- mean concentrations time plots (on both linear and semi-log scales) against nominal time post dose by day (Days 1 and 7 plotted on the same graph), based on the summary of concentrations by day and time post dose.
- 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, with all days on the same graph).

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.

6.3. Baseline and Other Summaries and Analyses

Demographic data collected at screening will be reported as part of the standard baseline summary tables. A breakdown of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by treatment in accordance with the sponsor reporting standards.

Subject evaluation groups will show end of study subject disposition. The table will present counts of subjects who were analyzed for PK and for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

6.4. Safety Summaries and Analyses

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-06835919.

No formal analyses are planned for safety data. The safety endpoints detailed in Section 3.4 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.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted.

6.4.1. Adverse Events

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

6.4.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.4.2.

6.4.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment and time postdose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.4.3.

Mean changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted separately for 0 hr pre-dose and 1 hr post-dose time points against days of collection. On each plot there will be 1 line for each treatment, both PF-06835919 and placebo on the same plot. Corresponding individual plots of changes from baseline will also be produced for each treatment.

For supine systolic and diastolic blood pressure and pulse rate, the differences between PF-06835919 and placebo (dose – placebo) will be summarized (N, mean, 90% CI) and plotted (mean) for each timepoint (including baseline).

Maximum absolute values and changes from baseline for vital signs will be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Maximum increase or decrease in vital signs will also be summarized; all planned and unplanned postdose timepoints will be included in these summaries.

6.4.4. Electrocardiograms

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment and time postdose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.4.4.

Mean changes from baseline in pre-dose QT, heart rate and QTcF will be plotted against days of collection. On each plot there will be 1 line for each treatment, Both PF-06835919 and placebo on the same plot. 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.

In addition for QTcF, heart rate and QT, the differences between PF-06835919 and placebo (dose – placebo) will be summarized and plotted (N, mean, 90% CI) for each timepoint (including baseline).

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

The number of subjects with corrected (QTcF) and uncorrected single post-dose QT values ≥500 msec will be listed.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Available safety and PK data may be reviewed.

8. APPENDIX 1

Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Categories for Maximum Post-dose QTcF (msec)				
All participants	≤450	450 - ≤480	480 - ≤500	>500
Categories for Maximum Increase from Baseline in QTcF (msec)				
All participants	≤30	30 - ≤60		>60

Categories for PR and QRS

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

Categories for Vital Signs

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

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