Protocol C0251007

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, THIRD-PARTY OPEN, PLACEBO-CONTROLLED, STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING A SINGLE DOSE OF PF-06823859 IN HEALTHY CHINESE PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: 2

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 16 Aug 2021	Original 25 Jun 2021	N/A	N/A
2 9 Jun 2022	Amendment 1 10 May 2022	To allow additional participants to be enrolled in the study in the event of participants' PK samples are considered to be non-evaluable with respect to the primary PK objective.	Section 2.2 The following statement was updated: Original statement: If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, participants may be replaced at the discretion of the investigator upon alignment with the sponsor. Updated statement: If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit. For participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, their PK sample collection will stop for ethic consideration.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C0251007. 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.

The purpose of this study is to evaluate the single-dose PK, safety, and tolerability of PF-06823859 after single IV administration to healthy adult Chinese participants. The information of PK, safety, and tolerability in healthy Chinese participants is being collected to support future PF-06823859 clinical development as well as drug registration in China.

2.1. Study Objectives, Endpoints, and Estimands

The followings are objectives and endpoints in this study. Estimands framework does not apply to this phase I study.

Objectives	Endpoints
Primary:	Primary:
• To evaluate the PK profile of single IV dose of 900 mg PF-06823859 in healthy Chinese participants. • To determine the safety and tolerability of single IV dose of 900 mg PF-06823859 in healthy Chinese participants.	• Serum PF-06823859 primary PK parameters, as permitted by data: C_{max}, T_{max}, AUC_{14day}, AUC_{28day}, AUC_{inf}, and $t_{½}$, • Assessments of AEs/SAEs including infusion site reactions and viral infections, vital signs, ECGs and laboratory tests.
Secondary:	Secondary:
• To further evaluate the PK of PF-06823859. • To evaluate the immunogenicity of PF-06823859.	• Serum PF-06823859 PK parameters, as permitted by data: C_{max} (dn), AUC_{last}, AUC_{last} (dn), AUC_{inf} (dn), CL, V_z, and MRT. • Incidence of the development of ADA and Nab.

2.2. Study Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the PK, safety, and tolerability following a single dose of PF-06823859 (900 mg) in healthy Chinese participants.

Approximately 12 participants will be enrolled into the study. Approximately 10 participants will be randomized to PF-06823859 and approximately 2 participants will be randomized to placebo.

If more than 2 participants discontinue or withdraw before completing at least the follow-up visit at Day 100, or if there are participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, additional participants may be enrolled upon alignment between the sponsor and the investigator such that approximate 10 participants could provide evaluable PK samples for no less than Day 100 follow-up visit. For participants whose PK samples are considered to be non-evaluable with respect to the primary PK objective, their PK sample collection will be stopped for ethic consideration.

Within 28 days of successful completion of the screening process, eligible participants will be enrolled and randomized to receive a single IV infusion of PF-06823859 or placebo. Participants will be admitted into the CRU approximately 1 day prior to dosing and are required to remain in the CRU through completion of Day 5 evaluations. Participants will return to the CRU for outpatient follow-up visits through Day 157.

ADA levels will be monitored from samples collected at the times specified in the SoA. Samples found to be positive will be further evaluated for NAb. Participants with positive results may be requested to return for additional follow-up for up to approximately 3 months after the last scheduled follow-up visit.

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the safety, PK, and immunogenicity data through Day 28 after treatment administration to preliminarily assess any ethnic differences between Chinese and non-Chinese to support China joining future global PF-06823859 clinical development.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Serum PF-06823859 primary PK parameters, as permitted by data: C_{max}, T_{max}, AUC_{14day}, AUC_{28day}, AUC_{inf}, and $t_{½}$,
- Assessments of AEs/SAEs including infusion site reactions and viral infections, vital signs, ECGs and laboratory tests.

3.2. Secondary Endpoint(s)

- Serum PF-06823859 PK parameters, as permitted by data: C_{max} (dn), AUC_{last}, AUC_{last} (dn), AUC_{inf} (dn), CL, V_z, and MRT.
- Incidence of the development of ADA and Nab.

3.3. Other Endpoint(s)

Not applicable.

3.4. Baseline Variables

The baseline value for laboratory, 12-Lead ECG and vital signs is defined as the latest measurement prior to taking dose.

3.5. Safety Endpoints

3.5.1. Adverse Events

Any events occurring following start of treatment will be counted as treatment emergent.

3.5.2. Laboratory Data

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

To determine if there are any clinically significant laboratory abnormalities, the hematological, 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.

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 unblinding and releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	Description
Safety Analysis Set	All randomized participants who received at least 1 dose of the study intervention
PK Concentration Set	All randomized participants who received at least 1 dose of study intervention and at least 1 concentration value is reported
PK Parameter Set	All randomized participants who received at least 1 dose of study intervention and at least 1 of the PK parameters is calculated
Immunogenicity Analysis Set	All randomized participants who received at least 1 dose of study intervention with at least 1 post-treatment anti-drug antibody determination

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no stasistical hypotheses for this study.

5.2. General Methods

No formal statistical tests will be performed. Descriptive summaries will be provided for all endpoints by treatment group.

5.2.1. Analyses for Binary Endpoints

Not applicable.

5.2.2. Analyses for Continuous Endpoints

Not applicable.

5.2.3. Analyses for Categorical Endpoints

Not applicable.

5.2.4. Analyses for Time-to-Event Endpoints

Not applicable.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Concentrations

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 the listings BLQ values will be reported as "<LLQ", where lower limit of quantification (LLQ) will be replaced with the value for the lower limit of quantification.

Deviations, missing concentrations and anomalous values

Subjects who experience events that may affect their PK profile (eg, due to known loss of drug during IV administration) may be excluded from the PK analysis.

In summary tables and plots of mean and median profiles of PK, statistics will be calculated having setting 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 PK analyst.

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

5.3.2. 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 not be presented if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as incomplete SC injection), 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. Pharmacokinetic Analysis

6.1.1. Pharmacokinetic Parameters

The PK parameters for PF-06823859 following single dose administration will be derived from the concentration-time profiles by noncompartmental analysis and summarized descriptively.

The PK parameter analysis will be carried out with PK parameter analysis set.

Calculation of PK parameters

Parameter	Definition	Method of determination
C_{max}	Maximum serum concentration	Observed directly from data
C_{max} (dn)	Dose normalized C_{max}	C_{max}/dose
T_{max}	Time at which C_{max} occurs	Observed directly from data as time of first occurrence
AUC_{inf}[a]	Area under the serum concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time Point estimated from the log-linear regression analysis
AUC_{inf} (dn) [a]	Dose normalized AUC_{inf}	AUC_{inf} /Dose
AUC_{last}	Area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{last} (dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{14day}	Area under the concentration-time profile from time zero to 14 days post-dose (336 hours)	Linear/Log trapezoidal method

Parameter	Definition	Method of determination
AUC_{28day}	Area under the concentration-time profile from time zero to 28 days post-dose (672 hours)	Linear/Log trapezoidal method
$t_{½}$[a]	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[a]	Clearance	$Dose/AUC_{inf}$
Vz	Volume of distribution	$Dose/(AUC_{inf}*k_{el})$
MRT[a]	Mean residence time	$AUMC_{inf}/AUC_{inf}$ -DOF/2, where $AUMC_{inf}$ is the area under the moment curve from time 0 extrapolated to infinity and DOF is the duration of the IV infusion.

a. if data permitted

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

Summary statsitics will be provided for these PK parameters as summarized below:

Parameter	Summary statistics
AUC_{last}, AUClast(dn), AUC_{inf}, AUC_{inf}(dn), AUC_{14day}, AUC_{28day}, C_{max}, C_{max}(dn), CL, V_z, MRT	N, arithmetic mean, median, coefficient of variation (CV)%, standard deviation (SD), minimum, maximum, geometric mean and geometric CV%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, CV%, SD, minimum, Maximum.

Box and whisker plots for individual subject parameters (AUC_{last}, AUC_{last}(dn), AUC_{inf}, AUC_{inf}(dn), AUC_{14day}, AUC_{28day}, C_{max} and C_{max}(dn)) will be presented and overlaid with geometric means.

6.1.2. Pharmacokinetic Concentrations

Presentations for PF-06823859 concentrations will include:

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

- a summary of concentrations by nominal time postdose, where the set of statistics will include n, mean, median, SD, CV, minimum, maximum and the number of concentations above the LLQ.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose.
- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose.
- Individual concentrations time plots (on both linear and semi-log scales) against actual time postdose.
- Individual concentrations time plots by participant (on both linear and semi-log scales) agains actual time postdose (there will be separate plots for each participant 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-06823859 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 participant plots by time, the actual PK sampling time will be used.

These analyses will be carried out with PK concentration analysis set.

6.2. Immunogenicity Analysis

Overall incidence of development of ADA, NAb will be calculated and summarized by treatment and time points specified in the SoA. Participants level immune response will also be summarized by treatment. Effect of positive ADA and neutralizing immune response on safety and PK may be assessed, if appropriate.

6.3. Subset Analyses

Not applicable.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

Demographic and baseline characeteristics will be summarized descriptively.

6.4.2. Study Conduct and Participant Disposition

A subject disposition table will be provided. Subject disposition will be summarized and will include the number and percentage of participants randomized, treated, completing and discontinuing from the study, the number of participants in each analysis population and reasons for discontinuation of study. The percentages will use the number of randomized as the denominator.

6.5. Safety Summaries and Analyses

6.5.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards. Adverse events related to COVID-19 will be summarized.

6.5.2. Laboratory Data

Laboratory data will be summarized using Pfizer's implementation of CDISC standards. Change from baseline will also be summarized by treatment and visit.

Incidence of laboratory test abnormalities (without regard to baseline abnormality) will be summarized.

6.5.3. Vital Signs

Vital signs will be summarized using Pfizer's implementation of CDISC standards. For each planned timepoint, absolute values and change from baseline values will be summarized with descriptive statistics.

Maximum absolute values and maximum change from baseline for vital signs will also be summarized descriptively by treatment using categories. Numbers and percentages of participants meeting the categorical criteria will be provided by treatment and individual values listed.

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

6.5.4. Electrocardiograms

Baseline and changes from baseline for the ECG parameters heart rate, QT interval, QTc interval, PR interal and QRS interval will be summarized by treatment and time.

The number and percentages of participants with maximum postdose QTc values and maximum increases from baseline in the following categorie will be tabulated by treatment:

Safety QTc Assessment

Degree of prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450- <480	>480-500	>500
Increase from baseline		30-60	>60

6.5.5. Other Safety Data

Incidence of viral infections or change in baseline of viral loads (CMV, VZV, EBV, HHV6, and HSV-1/2) if they occur, will be summarized by treatment group.

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.

All concomitant medications as well as non-drug treatments will be provided in the listings.

The safety analyses will be analyzed using the safety analysis set.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study.

8. REFERENCES

Not applicable.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
ADA	antidrug antibodies
AE	adverse event
AUC	area under the curve
AUC_{14day}	AUC from time 0 to 14 days post-dose
AUC_{28day}	AUC from time 0 to 28 days post-dose
AUC_{inf}	AUC from time 0 extrapolated to infinite time
AUC_{last}	AUC from time 0 to the time of the last quantifiable concentration
$AUMC_{inf}$	area under the moment curve from time 0 extrapolated to infinity
BLQ	Below the limit of quantification
BP	blood pressure
bpm	beats per minute
CL	clearance
C_{max}	maximum observed concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRU	clinical research unit
dn	dose normalized
DOF	duration of the IV infusion
EBV	Epstein Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
HHV6	Human Herpes Virus 6
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
ID	identification
IV	intravenous
k_{el}	terminal phase rate constant
LLQ	lower limit of quantification
MRT	mean residence time
N/A	not applicable
NAb	neutralizing antibodies
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PR	pulse rate
QTc	corrected QT
QTcF	corrected QT (Fridericia method)

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SoA	schedule of activities
TEAE	treatment emergent adverse event
$t_{½}$	terminal phase half-life
T_{max}	time to reach C_{max}
V_z	volume at distribution
VZV	varicella-zoster virus