Protocol C4671016

A PHASE 1, SINGLE CENTER, OPEN-LABEL STUDY OF PF-07321332 ADMINISTERED IN COMBINATION WITH RITONAVIR AS REPEATED DOSES IN HEALTHY CHINESE PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 1

Date: 16 Nov 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 16 Nov 2021	Original 27 Sep 2021	N/A	N/A

2. INTRODUCTION

The purpose of the study is to investigate the PK, safety and tolerability of PF-07321332 following repeated oral doses in combination with a PK boosting agent ritonavir in Chinese healthy adults. One (or more) suitable Western study(ies) will be selected for comparison between Western and Chinese population. This may involve comparison of Day 1 data and/or steady state data (generally reached by Day 2) with the data obtained from the Chinese Phase 1 study. The comparison results will be used to bridge global clinical data and support China registration of PF-07321332.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4671016. 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

There are no estimands for this study.

Objectives	*Endpoints*
Primary:	***Primary:***
• *To characterize the plasma PK of PF-07321332 when PF-07321332/ritonavir is administered in healthy Chinese participants*	• *PF-07321332 plasma PK parameters:* • *Day 1: C_{max}, T_{max}, AUC_{12}* • *Day 5, 8,10 (pre-dose and 12 hours after last dose): C_{trough}* • *Day 10: C_{max}, T_{max}, AUC_{tau}; and if data permit, AUC_{last}, C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F, V_z/F and $t_{½}$*
Secondary:	***Secondary:***
• *To determine the safety and tolerability of PF-07321332/ritonavir in healthy Chinese participants after dose administration* • *To characterize the plasma PK of ritonavir following PF-07321332/ritonavir administration in healthy Chinese participants*	• *AEs, clinical safety laboratory tests, vital signs, 12-lead ECGs* • *Ritonavir plasma PK parameters:* • *Day 1: C_{max}, T_{max}, AUC_{12}* • *Day 5, 8,10 (pre-dose and 12 hours after last dose): C_{trough}* • *Day 10: C_{max}, T_{max}, AUC_{tau}; and if data permit, AUC_{last}, C_{av}, CL/F, V_z/F and $t_{½}$*
CCI [redacted]	[redacted]
[redacted]	[redacted]

2.2. Study Design

This is a Phase 1, open-label study to estimate the PK, safety and tolerability of PF-07321332 when PF-07321332/ritonavir is administered in healthy Chinese participants. The study will consist of 1 treatment: 10-day oral doses of 300 mg PF 07321332/100 mg ritonavir. A total of approximately 14 healthy male and/or female participants will be enrolled into the study to ensure at least 12 participants will complete the study. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the Investigator.

The total duration of participation in this study is approximately 73 days, including a screening period of up to 28 days to confirm eligibility, treatment duration about 12 days (10 days of dose duration and another 2 days of full PK profile duration) and a follow-up period of approximately 28-35 days post the last dose of study intervention.

All of participants will receive PF-07321332 and ritonavir together. The dose regimen is PF-07321332/ritonavir 300/100 mg q12h for a total of 19 oral doses (Day 1 to Day 10). The first dose and the last dose will be recommended to be administrated on Day 1 and Day 10 morning, respectively, for intensive PK sample collection feasibility. The evening dose will not be given on Day 10.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

As listed in Section 2.1 the primary endpoints (PF-07321332 plasma PK) as well as the secondary (ritonavir plasma PK) CCI [redacted] are related to PK and are described herein.

Samples for the PK analysis of PF-07321332 and ritonavir will be taken according to the schedule of activities (SoA) given in the protocol.

The PK parameters of PF-07321332 and ritonavir will be derived (if data permit) from the concentration-time data using standard non-compartmental methods. Plasma CCI [redacted] PK parameters are described in Table 2. 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 time will be used in the derivation of PK parameters.

Table 2. Plasma CCI [redacted] PK Parameters

Parameter	*Analyte*	*Day(s)*	*Definition*	*Method of Determination*
AUC_{last}[a]	*PF-07321332/ ritonavir*	*10*	*Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})*	*Linear/Log trapezoidal method.*
AUC_{12}	*PF-07321332/ ritonavir*	*1*	*Area under the plasma concentration-time profile from time 0 to time point on 12 hours, on Day 1*	*Linear/Log trapezoidal method.*
AUC_{tau}	*PF-07321332/ ritonavir*	*10*	*Area under the plasma concentration-time profile from time 0 to the time of the end of the dosing interval (tau), where tau=12 hours*	*Linear/Log trapezoidal method.*
C_{max}	*PF-07321332/ ritonavir*	*1, 10*	*Maximum plasma concentration during the dosing interval*	*Observed directly from data.*
T_{max}	*PF-07321332/ ritonavir*	*1,10*	*Time for C_{max}*	*Observed directly from data as time of first occurrence.*
$T_{½}$[a]	*PF-07321332/ ritonavir*	*10*	*Terminal elimination 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. Only those data points judged to describe the terminal log-linear decline will be used in the regression.*
CL/F[a]	*PF-07321332/ ritonavir*	*10*	*Apparent clearance*	*$Dose/AUC_{tau}$.*
V_z/F[a]	*PF-07321332/ ritonavir*	*10*	*Apparent volume of distribution*	*$Dose/(AUC_{tau} \times k_{el})$.*

Table 2. Plasma CCI PK Parameters

Parameter	*Analyte*	*Day(s)*	*Definition*	*Method of Determination*
C_{trough}	*PF-07321332/ ritonavir*	*5, 8, 10*	*Pre-dose concentration*	*Observed directly from data, pre-dose and 12 hours after last dose for Day 10.*
C_{av}[a]	*PF-07321332/ ritonavir*	*10*	*Average concentration*	*AUC_{tau} (Day 10) /12 hours.*
R_{ac}[a]	*PF-07321332*	*10*	*Accumulation ratio for AUC_{tau} following multiple dosing*	*AUC_{tau} (Day 10) /AUC_{12} (Day 1).*
$R_{ac,Cmax}$*	*PF-07321332*	*10*	*Accumulation ratio for C_{max}*	*C_{max} (Day 10) /C_{max} (Day 1).*
*PTR**	*PF-07321332*	*10*	*Peak-to-trough ratio*	*C_{max} (Day 10) /C_{trough} (Day 10), at steady state.*
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a. As data permit.

3.1. Primary Endpoint(s)

The primary endpoints are the PF-7321332 plasma PK parameters described in Table 2.

3.2. Secondary Endpoint(s)

The secondary endpoints include safety endpoints and the ritonavir plasma PK parameters, which are described in Section 3.5 and Table 2, respectievly.

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3.4. Baseline Variables

There are no baseline variables to be used as covariates or stratification factors in this study.

Baseline values are those collected on Day 1 prior to the first dosing, or the last pre-dose measurement collected on Day -1.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first

dosing day and time/start time, if collected, but before the end of the study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. Baseline is defined as the last pre-dose measurement collected on Day -1.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum), urinalysis, coagulation, TSH and T4 tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

3.5.3. Vital Signs Data

Blood pressure, pulse rate, respiratory rate and temperature will be taken at times detailed in the SoA given in the protocol. Baseline is defined as the last pre-dose measurement collected on Day 1. Change from baseline in supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be determined.

3.5.4. ECG Results

Triplicate 12-lead ECGs will be obtained at each assessment time indicated in the SoA given in the protocol. 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 on Day 1. Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be determined.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	***Description***
Enrolled/Randomly assigned to study intervention	*"Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
PK Concentration Analysis Set	*The PK concentration population* for an analyte *is defined as all participants assigned to investigational product and treated who have at least 1 concentration measured.*

Participant Analysis Set	***Description***
Enrolled/Randomly assigned to study intervention	*"Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
PK Parameter Analysis Set	*The PK parameter analysis population* for an analyte *is defined as all participants assigned to investigational product and treated who have at least 1 of the PK parameters of primary interest measured.*
Safety Analysis Set	*All participants enrolled 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

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

All data will be descriptively summarized.

Binary and categorical variables will be presented using summary statistics: number of observations and percentages.

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation (SD), coefficient of variation (cv%), median, minimum, maximum, geometric mean and geometric cv%.

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. Pharmacokinetic Data

Concentrations Below the Limit of Quantification

In all PK 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 (LLQ).)

Deviations, Missing Concentrations and Anomalous Values

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

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., 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 participant's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a participant 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 participant has a known biased estimate of a PK parameter (e.g., due 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.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The PK parameters detailed in Section 3.1 will be listed and descriptively summarized for participants in the PK parameter analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.2. For each analyte (PF-07321332 plasma, CCI [redacted] and ritonavir plasma), the PK parameters will be summarized by study day. Each summary will include the set of summary statistics as specified in Table 3.

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
C_{max}, AUC_{12}, C_{trough}, AUC_{tau}, AUC_{last}, C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F, V_z/F, CCI	N, arithmetic mean, median, cv%, SD, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{½}$	N, arithmetic mean, median, SD, minimum, maximum.

For AUCs and C_{max}, box and whisker plots for individual participant parameters overlaid with geometric means will be plotted for each analyte. For C_{max}, box and whisker plots will be presented with both Days 1 and 10 on the same figure by analyte. C_{trough} over time will be plotted for each analyte. Supporting data from the estimation of $t_{½}$ will be listed by analyte where applicable.

For each analyte, the PK concentrations will be presented using participants in the PK concentration analysis set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by participant ID 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 and nominal time post-dose, where the set of statistics will include n, mean, median, SD, cv%, minimum, maximum and the number of concentrations above the LLQ.
- median concentration-time plots (on both linear and semi-log scales) against nominal time post-dose.
- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose.
- individual concentration-time plots by dose (on both linear and semi-log scales) against actual time post-dose.

All figures (individual, mean, and median) will be presented with both Days 1 and 10 on the same figures. The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long PF-07321332 and ritonavir concentrations are quantifiable.

The PK parameters of PF-07321332 and ritonavir on Day 1 and steady state obtained from this study will be used to compare with the corresponding PK parameters obtained from Studies C4671014 and C4671015 to evaluate the PK characteristics between Chinese and Western populations. These analyses and results will be presented separately from the clinical study report (eg, ethnic sensitivity analysis report or other appropriate documents).

6.2. Secondary Endpoint(s)

The detailes of safety analyses are described in Section 6.6.

The ritonavir plasma PK will be summarized and plotted the same as the primary endpoints described in Section 6.1.

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6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demograohic and baseline characteristics collected prior to the first dosing will be summarized following the sponsor reporting standard.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition. Frequency counts and percentages will be supplied for participant discontinuation(s). Data will be reported in accordance with the sponsor reporting standards.

6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

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

6.6.2. Laboratory Data

Laboratory data will be listed and summarized in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.5.2.

6.6.3. Vital Signs

Absolute values and changes from baseline in blood pressure, pulse rate, temperature and respiratory rate will be summarized by time, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Minimum and/or maximum absolute values and changes from baseline for vital signs endpoints (blood pressure and pulse rate) will also be summarized descriptively using categories as defined in Appendix 1. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

6.6.4. Electrocardiograms

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by time using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

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 participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

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

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

None.

9. APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤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
Seated pulse rate (bpm)	min. <40	max. >120

Appendix 2. List of Abbreviations

Abbreviation	Term
CCI [redacted]	[redacted]
Ae_{tau}%	percent of dose excreted in urine as unchanged drug
AUC	area under the concentration-time curve
AUC_{12}	AUC from time 0 to 12 hours
AUC_{last}	AUC from time 0 to T_{last}
AUC_{tau}	AUC from time 0 to time tau
BLQ	below the limit of quantitation
BP	blood pressure
C_{av}	average concentration
C_{max}	maximum observed concentration
C_{trough}	pre-dose concentration
CCI [redacted]	[redacted]
CL/F	apparent clearance
CV	coefficient of variation
ECG	electrocardiogram
ID	identification
LLQ	lower limit of quantitation
NC	not calculated
ND	not done
NS	not sample
N/A	not applicable
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PTR	peak-to-trough ratio
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
R_{ac}	accumulation ratio for AUC_{tau}
$R_{ac,Cmax}$	accumulation ratio for C_{max}
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$T_{1/2}$	terminal elimination half life
T4	thyroxine
T_{max}	time for C_{max}
TSH	thyroid stimulating hormone
TEAE	treatment-emergent adverse event
V_z/F	apparent volume of distribution