Protocol C5241018

A PHASE 1, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY FOLLOWING SINGLE AND MULTIPLE DOSES OF SISUNATOVIR IN CHINESE HEALTHY PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 08 Aug 2023

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

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 08 Aug 2023	Original 9 Jun 2023	N/A	N/A

2. INTRODUCTION

PF-07923568 (sisunatovir, formerly RV521) is being developed to act as a highly potent, selective, orally available agent to treat RSV infection. Sisunatovir is an inhibitor of RSV fusion (F) protein mediated fusion that is currently being investigated for the treatment of RSV infection.

The purpose of the study is to evaluate the PK, safety and tolerability of sisunatovir (PF-07923568) in Chinese healthy adult participants. This information is being collected to support further clinical development as well as drug registration in China.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5241018.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives, Endpoints, and Estimands

The following are the objectives and endpoints in this study. Estimand framework will not be applied to this Phase 1 study in healthy participants.

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Table 2. Study Objectives and Endpoints

Type	*Objectives*	*Endpoints*
	Primary:	***Primary:***
Pharmacokinetics	• *To evaluate the PK of sisunatovir after single dose and multiple doses in Chinese healthy participants*	*Sisunatovir plasma exposure for single and multiple doses:* • *Post dose on Day 1: C_{max}, AUC_{last}, AUC_{tau} (tau=12), and AUC_{inf} as data permit.* • *Post first dose on Day 4: C_{max}, AUC_{tau}* • *Post dose on Day 8: C_{max}, AUC_{tau}*
	Secondary:	***Secondary:***
Pharmacokinetics	• *To further characterize the PK profile of sisunatovir after single dose and multiple doses of sisunatovir in Chinese healthy participants*	*Additional sisunatovir plasma PK parameters:* • *Post dose on Day 1: T_{max}, $t_{½}$, MRT, V_z/F, and CL/F as data permit* • *Post first dose on Day 4: T_{max}* • *Post dose on Day 8: T_{max}, $t_{½}$, accumulation ratio on AUC_{tau} (R_{ac}) and on C_{max} ($R_{ac,Cmax}$), MRT, V_z/F, CL/F, C_{trough}, C_{av}, AUC_{last}, AUC_{inf} and PTR as data permit*
Safety	• *To evaluate the safety and tolerability of sisunatovir following single and multiple dose in Chinese healthy participants*	• *AEs/SAEs, clinical safety laboratory tests, vital signs, 12-lead ECGs*
	Tertiary/Exploratory:	***Tertiary/Exploratory:***
CCI [redacted]		
Pharmacokinetics	• *To explore PK of sisunatovir by microsampling technique, if feasible*	• *Concentration of sisunatovir from paired samples obtained via microsampling compared to plasma sampling (if possible)*

2.3. Study Design

This is a Phase 1, single-center, open-label and single-arm study to investigate PK, safety and tolerability of 200 mg sisunatovir given as a single dose on Day 1 in a fasted state followed by repeated twice daily doses (200 mg BID, Q12 hours) from Days 4-7 plus 1 morning dose on Day 8 in a fed state in Chinese healthy participants. Approximately 12 participants in total will be included in this study. If a participant discontinues before completing the study, or withdraws for reasons unrelated to the safety of the treatment, the participant may be replaced at the discretion of the investigator upon consultation with the sponsor.

The study will consist of a Screening visit, a Treatment period of single dosing (Day -1 to Day 3) and multiple dosing (Day 4 to Day 11), and a Follow-up contact. The total duration

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of participation from the Screening visit to the Follow-up contact will be up to approximately 71 days.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

As listed in Section 2.2, the primary endpoints are related to Sisunatovir plasma exposure after single and multiple doses, and are detailed in Table 3.

3.2. Secondary Endpoint(s)

The secondary endpoints are additional pharmacokinetics parameters after single and multiple doses of Sisunatovir as detailed in Table 3, as well as safety endpoints described in Section 3.5.

Table 3. Sisunatovir Plasma PK Parameter Definitions

Parameter	*Study Day*	*Definition*	*Method of Determination*
C_{max}	*1, 4, 8*	*Maximum observed concentration*	*Observed directly from data*
T_{max}	*1, 4, 8*	*Time to reach maximum concentration*	*Observed directly from data*
AUC_{inf}[β]	*1, 8*	*Area under the concentration-time curve from time 0 to infinity*	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} *is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis*
AUC_{last}	*1, 8*	*Area under the concentration-time curve from time 0 to the time of last quantifiable concentration*	*Linear/Log trapezoidal method*
AUC_{tau}	*1, 4, 8*	*Area under the concentration time curve from time 0 to the time of the end of the dosing interval (tau), where tau=12 hours*	*Linear/Log trapezoidal method.*
$t_{½}$[α]	*1, 8*	*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*
MRT[α]	*1, 8*	*Mean residence time*	*Day 1:* $MRT = AUMC_{inf}/AUC_{inf}$ *Day 8:* $[AUMC_{tau} + tau(AUC_{inf} - AUC_{tau})]/AUC_{tau}$ where $AUMC_{inf}$ *is the area under the first moment curve from zero time to infinity* $AUMC_{tau}$ *is area under the first moment curve over the dosing interval tau.*

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Table 3. Sisunatovir Plasma PK Parameter Definitions

Parameter	*Study Day*	*Definition*	*Method of Determination*
V_z/F^a	*1*	*Apparent volume of distribution*	*Dose/(AUC_{inf} × k_{el})*
CL/F^a	*1, 8*	*Apparent oral clearance*	*Dose/AUC_{inf}*
$R_{ac}{}^a$	*8*	*Accumulation ratio on AUC_{tau}*	*AUC_{12} (Day 8) /AUC_{12} (Day 4)*
$R_{ac,Cmax}{}^a$	*8*	*Accumulation ratio on C_{max}*	*C_{max} (Day 8) /C_{max} (Day 4)*
C_{trough}	*6, 7, 8*	*Lowest concentration observed during the dosing interval*	*Observed directly from data*
C_{av}	*8*	*Average concentration at steady state*	*AUC_{12} (Day 8) /12 hours.*
V_z/F^a	*8*	*Apparent volume of distribution at steady state*	*V_z/F = Dose/(AUC_{tau} × k_{el})*
PTR	*8*	*Peak-trough ratio*	*C_{max}/C_{trough}*

a. If data permit.

3.3. Other Endpoint(s)

The following exploratory endpoints are defined in this study:

- CCI [redacted]
- *Concentration of sisunatovir from paired samples obtained via microsampling compared to plasma sampling (if possible).*

3.4. Baseline Variables

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

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.5. Safety Endpoints

The following data will be considered in standard safety summaries (see protocol for collection days, assessment procedures, and list of parameters):

- Adverse events (AE) / Serious adverse events (SAE)
- Laboratory tests data
- Vital signs data
- 12-lead ECG results

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset which was occurred before the first treatment dosing. Events

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that occur during follow-up within the lag time of up to 28-35 days after the last dose of study intervention will be counted as treatment emergent and attributed to the last treatment taken. Events that occur during the washout period between study periods will be counted as treatment emergent and attributed to the previous treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent. 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.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards.The baseline measurement is the value collected on Day -1 prior to the treatment start, or the last pre-dose measurement collected if the Day -1 measurement is not available.

3.5.3. Vital Signs

Supine blood pressure (BP), pulse rate (PR) and temperature will be measured at times specified in the SoA given in the protocol.

The baseline measurement is the predose measurement on Day 1 or the last predose measurement collected if the Day 1 measurement is not available.

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 will then be selected, except in the case where a participant 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 participant does not show a decrease, the minimum increase should be taken.

3.5.4. Electrocardiograms

A 12-lead ECG will be obtained at specified day and timepoint as indicated in the SoA of the protocol. If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

QTcF = QT / (RR)^(1/3) where RR = 60/HR (if not provided)

The baseline value is the predose measurement on Day 1 or the last predose measurement collected if the Day 1 measurement is not available.

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 respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

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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.

The following analysis set are defined in this study:

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention.*
PK Concentration Analysis Set	*The PK concentration analysis set is defined as all participants who take at least 1 dose of study intervention and in whom at least 1 plasma concentration value is reported.*
PK Parameter Analysis Set	*The PK parameter analysis set is defined as all participants who take at least 1 dose of study intervention and have at least 1 of the PK parameters of interest calculated.*
Safety analysis set	*All participants who take at least 1 dose of study intervention.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following the last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

Descriptive analyses will be performed. Some measures will be summarized using graphical representations.

Summaries by treatment will include summaries by administrated dose and fed/fasted condition, when applicable.

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the sponsor reporting standards.

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the sponsor reporting standards. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

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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 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 mean/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 as 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.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst or pharmacokineticist.

PK 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 (ie, 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 treatment with ≥3 evaluable measurements. PK parameter analyses will not be performed for a particular parameter if more than 50% of the data are NC.

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 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.

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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. The PK parameters will be summarized by study day. Each summary will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
C_{max}, AUC_{last}, AUC_{tau}, AUC_{inf}, MRT, V_z/F, CL/F, R_{ac}, $R_{ac,Cmax}$, C_{trough}, C_{av}, PTR	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 AUC_{last}, AUC_{tau}, AUC_{inf}, and C_{max}, box and whisker plots for individual participant parameters overlaid with geometric means will be plotted by day and be presented in the same figure. for each analyte.

6.2. Secondary Endpoint(s)

6.2.1. Secondary PK Endpoints

Analyses similar to those planned for the primary PK endpoints will be used for the secondary PK endpoints using the summary statistics as specified in Table 4. The summaries will be presented by study day.

PK concentration summaries:

Presentation for the plasma concentrations of sisunatovir will be generated using the PK concentration analysis set (as defined in Section 4) including:

- a listing of all concentrations sorted by participant ID, study 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 study day and nominal time post-dose, where the set of statistics will include n, mean, median, SD, cv%, minimum, maximum and the number of concentrations that are above or equal to the LLQ.
- median concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by study day in the same figure.

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- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by study day in the same figure.

- individual concentration-time plots (on both linear and semi-log scales) against actual time post-dose for all subjects in the same figure (there will be separate spaghetti plots paged by study day per scale).

6.3. Other Endpoints

CCI

[redacted]

6.3.2. PK Concentration of sisunatovir from paired samples obtained via microsampling compared to venous sampling

Cmax and AUCtau derived from blood samples collected using the Tasso® M20 device adjusted for B/P ratio will be summarized for sisunatovir and will inlucde the set of summary statistics as sepecified in Table 4. Summary statistics (N, geometric mean, geometric CV, median, arithmetic mean, CV, minimum, maximum) of the whole blood concentrations, plasma equivalent concentrations by microsampling using individual B/P ratio and plasma equivalent concentration by microsampling using population geometric mean B/P ratio at nominal time of collection as defined in SoA of the protocol for each treatment arm will be calculated.

Furthermore, to determine correlation in concentrations derived from time matched Tasso® M20 microsampling (calculated using individual or population) and traditional venous plasma sampling, Bland-Altman plot analysis will be performed to evaluate the bias and SD of the bias between the mean differences and to estimate an agreement interval within a 95% confidence limit. Plots of the difference between the two samples (on Y-axis) as a function of the average of the two samples (on X-axis). These plots will be colored by participant in addition to by timepoint. In addition, a correlation plot of the plasma PK sample (on X-axis) and Tasso PK sample (on Y-axis) will be created including a line of equality Y = X.

These results will be reported in a separate Clinical Bioanalytics summary report and may not be included in the CSR.

6.4. Subset Analyses

No subset analyses will be performed.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics collected prior to the first dosing will be summarized following the sponsor reporting standard. BMI will be derived using the following formula: $BMI = weight\ (kg)/[height(m)]^2$.

6.5.2. Study Conduct and Participant Disposition

A summary for participant disposition will be generated by period. 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. Study Treatment Exposure

Study treatment exposure will be listed.

6.5.4. Prior, Concomitant Medications and Nondrug Treatments

All prior, 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

All safety analyses will be performed on the Safety Analysis Set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination 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. Demographic data collected at screening will be reported.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards. All AEs will be listed. TEAEs will be presented with high-level summay, summary by System Organ Class (SOC) and Preferred Term (PT).

6.6.2. Laboratory Data

Laboratory data will be listed and summarized in accordance with the sponsor reporting standards. Laboratory test abnormality will be summarized (with or without regard to baseline abnormality). Baseline is as defined in Section 3.5.2.

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6.6.3. Vital Signs

Absolute values and changes from baseline in blood pressure, pulse rate, and temperature will be listed and summarized by study day and time post-dose, according to sponsor reporting standards. Baseline is as defined in Section 3.5.3.

Numbers and percentages of participants meeting the categorical criteria as defined in Section 9.1 Appendix 1 will be summarized. All planned and unplanned post-dose time points will be counted in the categorical summary.

6.6.4. Electrocardiograms

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

Categorical summaries for QTcF, PR interval, and QRS meeting the criteria as defined in Section 9.1 Appendix 1 will be summarized.All planned and unplanned post-dose time points will be counted in the categorical summary.

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

7. INTERIM ANALYSES

7.1. Introduction

There will be no interim analysis in this study.

7.2. Interim Analyses and Summaries

None.

8. REFERENCES

None.

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9. APPENDICES

9.1. Appendix 1: Categorical Classes for ECG and Vital Signs

Categories for QTcF

Maximum absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Maximum increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR interval and QRS

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

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
Pulse rate (bpm)	min. <40	max. >120

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9.3. Appendix 3: List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the curve
BLQ	below the limit of quantitation
BP	blood pressure
C_{av}	average concentration
CI	confidence interval
C_{max}	maximum observed concentration
CL/F	apparent clearance
CRF	case report form
C_{trough}	pre-dose concentration
CV	coefficient of variation
ECG	electrocardiogram
LLQ	lower limit of quantitation
MRT	mean residence time
NC	not calculated
ND	not done
NS	No sample
PK	pharmacokinetic(s)
PR	Pulse rate
PT	preferred term
PTR	peak-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}
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOC	System organ class
TEAE	Treatment-emergent adver event
V_z/F	apparent volume of distribution

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