Protocol *C5241012*

A Phase 1, open-label, single-dose, parallel group study to compare the pharmacokinetics and safety of PF-07923568 in adult participants with varying degrees of hepatic impairment relative to participants without hepatic impairment

Statistical Analysis Plan
(SAP)

Version: 1.0

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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 / 19 May 2023	Original 23 Feb 2023	N/A	N/A

2. INTRODUCTION

PF-07923568 (sisunatovir) is being developed to act as a highly potent, selective, orally available agent to treat and prevent RSV infection. PF-07923568 is an inhibitor of CCI [redacted] *that is currently being investigated for the treatment of RSV infection.*

The primary purpose of this study is to characterize the effect of varying degrees of HI on the plasma PK of PF-07923568 following administration of a single oral dose of PF-07923568.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5241012.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	*Endpoints*
Primary:	***Primary:***
• *To compare the PK of PF-07923568 following administration of a single oral dose in adult participants with varying degrees of HI relative to age- and body weight-matched participants without HI.*	• *Plasma: C_{max}, AUC_{last} or AUC_{inf}*, as data permit.*
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of a single oral dose of PF-07923568 when administered to adult participants with varying degrees of HI and in age- and body weight-matched participants without HI.*	• *Assessment of TEAEs, clinical laboratory abnormalities, VS, ECG parameters.*
Other:	***Other:***
• *To compare additional PK parameters of PF-07923568 following administration of a single oral dose in adult participants with varying degrees of HI and in age- and body weight-matched participants without HI.*	• *Plasma: CL/F, V_z/F, T_{max} and $t_{1/2}$ as data permit.*

** AUC_{last} will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf}, otherwise they will be treated as tertiary endpoints.*

2.3. Study Design

This is an open-label, single-dose, parallel-group, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of PF-07923568 after a single, oral CCI *mg dose administered in the fed state (standard breakfast). A total of approximately 28-34 participants with varying degrees of hepatic function will be administered as a single, oral* CCI *mg dose of PF-07923568 in the fed state as shown in Table 2.*

Table 2. Hepatic Function Categories Based on Child-Pugh Score

Group	*Description*	*Child-Pugh Score*	*Number of Participants*
1	*Without HI*	*Not Applicable*	*8[a]*
2	*Mild HI*	*Class A (5 to 6 points)*	*8*
3	*Moderate HI*	*Class B (7 to 9 points)*	*8*
4	*Severe HI*	*Class C (10 to 15 points)*	*4-8[b]*

a. Additional participants may be dosed to a maximum of 10 participants to ensure mean age ±10 years and mean body weight ±15 kg of this group is aligned with the pooled average assessed when approximately ≥75% of participants are dosed across the other 3 groups.

b. The total number of participants enrolled that are classified as having severe HI will be a minimum of 4 to a maximum of 8 depending on recruitment rates.

Participants will be dosed in a staged manner as follows:

- *Participants with moderate HI (Group 3) and severe HI (Group 4) will be enrolled first.*
- *Recruitment of participants with mild HI (Group 2) will initiate when approximately 50% of the participants in Group 3 have been dosed.*
- ***Sponsor approval is required <u>before</u> proceeding with recruitment of Group 2.***
- *An average value for age and weight for the 3 HI groups (Groups 2-4) will be determined and participants without HI (Group 1) will be recruited to match the average demographics (at a minimum, age and weight, and as much as practically possible gender) across the pooled Groups 2-4.*
- *Recruitment for healthy participants in Group 1 (without HI) may start when approximately 75% of total participants across Groups 2-4 (ie, approximately 15 to 18 participants) have been dosed.*
- ***Sponsor approval is required <u>before</u> proceeding with recruitment of Group 1.***

Participants who prematurely discontinue before completing all assessments may be replaced, at the discretion of the investigator and sponsor study team.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are the plasma PK parameters including C_{max}, AUC_{last} or AUC_{inf}, as data permit.

The plasma PK parameters for PF-07923568 following single dose administration will be derived from the concentration-time profiles as detailed in Table 3. 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 3. Plasma PK Parameters

Parameter	***Definition***	***Method of Determination***
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})*	*Linear/Log trapezoidal method.*
AUC_{inf}*	*Area under the plasma concentration-time profile from time zero extrapolated to infinite time*	*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.*
C_{max}	*Maximum plasma concentration*	*Observed directly from data.*
T_{max}	*Time for C_{max}*	*Observed directly from data as time of first occurrence.*
$t_{1/2}$*	*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. Only those data points judged to describe the terminal log-linear decline will be used in the regression.*
*CL/F**	*Apparent clearance*	*Dose/AUC_{inf}.*
V_z/F*	*Apparent volume of distribution*	*Dose/(AUC_{inf}·k_{el}).*

** as data permit*

3.2. Secondary Endpoints

The secondary endpoints are the safety and tolerability data which are discussed in Section 3.5.

3.3. Other Endpoints

Other endpoints are the plasma PK parameters including T_{max}, CL/F, V_z/F, T_{max} and $t_{1/2}$ are defined in Table 3.

3.4. Baseline Variables

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

3.5. Safety Endpoints

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

- Adverse events (AE)
- Laboratory data
- Vital signs data
- ECG results

3.5.1. Adverse Events

The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent. 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 case report form data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Events that occur during follow-up within the lag time of up to 365 days after the last dose 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 haematological and clinical chemistry will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

The baseline measurement is the predose measurement on Day 1. Changes from baseline will be defined as the change between the postdose and baseline measurements.

3.5.3. Vital Signs

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

The baseline measurement is the predose measurement on Day 1. Changes from baseline will be defined as the change between the postdose and baseline measurements.

3.5.4. Electrocardiograms

QT interval, QTcF, PR, QRS and HR will be recorded at each assessment time indicated in the SoA given in 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 measurement is the predose measurement on Day 1. Changes from baseline will be defined as the change between the postdose and baseline measurements.

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 and classifications will be documented per standard operating procedures.

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. 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.*
Safety analysis set	*All participants assigned to study intervention and who take at least 1 dose of study intervention.*
PK Concentration Set	*The PK concentration population is defined as all participants who received at least 1 dose of PF-07923568 and in whom at least 1 plasma concentration value is reported.*
PK Parameter Set	*The PK parameter analysis population is defined as all participants who received at least 1 dose of PF-07923568 and have at least 1 of the PK parameters of interest calculated.*

5. GENERAL METHODOLOGY AND CONVENTIONS

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

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

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

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic 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.

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.

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 dose with ≥3 evaluable measurements.

If an individual participant 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.

5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

The effect of varying degrees of hepatic impairment on PK parameters will be assessed by constructing 90% CIs around the estimated difference between each of the Test (hepatic impaired) groups and the Reference (without hepatic impairment) group. A one-way ANOVA will be used to compare the natural log transformed PF-07923568 AUC_{inf}, C_{max}, and AUC_{last}, as data permit, for each of the hepatic impairment groups (Test) to the group without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test /Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Individual PF-07923568 concentrations will be listed and summarized descriptively by nominal PK sampling time and hepatic function group. Individual participant and summary profiles of the concentration-time data (using actual and nominal times, respectively) will be plotted by hepatic function group for total plasma PF-07923568.

Box and whisker plots for individual PK parameters (AUC_{inf}, AUC_{last}, and C_{max}, if data permit) will be constructed by hepatic function group and overlaid with geometric means. PK parameters of PF-07923568 will be summarized descriptively by hepatic function group.

Additional analysis using linear regression may be used to analyze the potential relationship between appropriate PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max}, if data permit) and hepatic function (eg, serum albumin concentration, PT or T bili). Plots of PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max}) versus hepatic function will be constructed, with a regression line and 90% confidence region included. Estimates of the slope and intercept, together with a 90%

CI, and the coefficient of determination (ie, R-squared and adj-R-squared) may be obtained from the model.

Additionally, as an exploratory analysis, age and body weight may be explored as additional covariates/factors in the models, as appropriate.

6.2. Secondary Endpoints

6.2.1. Safety Data

Safety data analyses and summaries are described in Section 6.6.

6.3. Other Endpoints

The plasma concentrations of PF-07923568 will be listed and descriptively summarized by nominal PK sampling time and hepatic function group on the PK Concentration Set. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted by hepatic function group using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Presentations of concentrations will include:

- A listing of all concentrations sorted by participant ID, hepatic function group and nominal time postdose. 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 hepatic function group and nominal time postdose, where the set of statistics will include n, mean, median, SD, %CV, minimum, maximum and the number of concentrations above the LLQ.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function group (all hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function group (all hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).

- Individual concentration time plots by hepatic function group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each hepatic function group per scale).

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all hepatic function groups) per scale].

The plasma PK parameters for PF-07923568 will be summarized descriptively by hepatic function group in accordance with Pfizer data standards on the PK Parameter Set, as data permit. Missing values will be handled as detailed in Section 5.3.1. Each PK parameter (Table 4) will be summarized by hepatic function group and will include the set of summary statistics as specified in Table 5.

Table 4. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-07923568
AUC_{last}	ln	A, D
AUC_{inf}*	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
$t_{1/2}$*	R	D
CL/F*	ln	D
V_z/F*	ln	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

Table 5. PK Parameters to be Summarized Descriptively by Hepatic Function Group

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, CL/F, V_z/F	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic Summaries

Demographic characteristics (age, gender, ethnicity, race, weight, height and body mass index) will be summarized by hepatic function group for enrolled population in accordance with the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by hepatic function group. Data will be reported in accordance with the CaPS.

6.5.3. Concomitant Medications and Nondrug Treatments

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

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 by hepatic function group, where appropriate.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by hepatic function group. Data will be reported in accordance with the CaPS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by hepatic function group in accordance with the CaPS.

6.6.3. Vital Signs

Vital sign data will be databased and available upon request.

6.6.4. Electrocardiograms

ECG data will be databased and available upon request.

7. INTERIM ANALYSES

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 modeling, and/or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
AUC_{24}	area under the concentration curve from time 0 to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinite time
$AUC_{inf,u}$	unbound AUC_{inf}
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of C_{last}
$AUC_{last,u}$	unbound AUC_{last}
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	CDISC and Pfizer Standards
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent clearance
C_{last}	predicted plasma concentration at the last quantifiable time point
C_{max}	maximum plasma concentration
$C_{max,u}$	unbound C_{max}
ECG	electrocardiogram
HR	heart rate
k_{el}	terminal phase rate constant
LLQ	lower limit of quantitation
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POPPK	population PK
PR	pulse rate
QRS	combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
RR	respiratory rate
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoA	schedule of activities
SOP	standard operating procedure
$t_{½}$	terminal phase half-life

Abbreviation	Term
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
V_z/F	apparent volume of distribution

Appendix 2. SAS code

An example of the PROC MIXED code is provided below:

```
proc mixed data = tab.pk covtest alpha=0.1;
        class group;
        model l&var = group / S covb alpha=0.1 CL DDFM=KR;
        repeated/ type=un subject=subjid group=group R;
        lsmeans group;
```

```
        estimate ' Mild HI vs Without HI'          group -1 1 0 0;
        estimate ' Moderate HI vs Without HI"      group -1 0 1 0;
        estimate ' Severe HI vs Without HI"        group -1 0 0 1;
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;
run;

/* Letter assignments for group within the estimate statement above are as follows;
A = Without HI' (Reference);
B = Mild HI (Test1)
C = Moderate HI (Test2)
D = Severe HI (Test3)
*/;
```

An example of the PROC REG code is provided below:

```
proc reg data=tab.pk;
        model l&var=clcr/clb alpha=0.1;
        ods output ParameterEstimates = param&var;
        ods output FitStatistics = fit&var;
        ods output ANOVA = reg&var;
run;
```