Protocol C5241006

A Phase 1, Randomized, Sponsor Open, Two-Part Crossover Study to Assess Safety, Tolerability, Pharmacokinetics and Food Effect of Multiple Doses in Part 1 and Palatability of a Single Dose of Sisunatovir in Part 2, in Healthy Adult Participants

Statistical Analysis Plan (SAP)

Version: 1

Date: 14 Feb 2023

[redacted]

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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 14 Feb 2023	Amendment 1 23 Dec 2022	N/A	N/A

2. INTRODUCTION

Sisunatovir (PF-07923568) is an orally administered RSV F-protein inhibitor being developed to target viral-host cell fusion for the treatment of adult and pediatric patients with RSV. This study is designed to assess safety and tolerability, pharmacokinetics, and food effect of multiple oral doses of sisunatovir. Additionally, the study is also designed to generate preliminary palatability data that will inform further development of formulations appropriate for pediatric Phase 2 and 3 studies.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C5241006.

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.

Objectives	***Endpoints***
Primary:	***Primary:***
• *To characterize the safety and tolerability of multiple oral doses of sisunatovir in healthy adult participants*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs*
Secondary:	***Secondary:***
• *To characterize the PK of multiple oral doses of sisunatovir*	• *PK Parameters AUC_{tau}, C_{max}, T_{max}, $AUC_{tau}(dn)$, $C_{max}(dn)$ for Day 1 and AUC_{tau}, C_{max}, T_{max}, $AUC_{tau}(dn)$, $C_{max}(dn)$, CL/F R_{ac}, $R_{ac,Cmax}$; and $t_{1/2}$ and V_z/F (if data permits) post last dose on Day 5*
• *To evaluate the effect of food on the PK of multiple oral doses of sisunatovir*	• *The ratio of AUC_{tau} and C_{max}, on Day 5; T_{max} on Day 5*
• *To characterize the impact of liquid vehicles on the palatability of sisunatovir*	• *Palatability Assessment Questionnaire Scoring Metrics: mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking*
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2.3. Study Design

This is a Phase 1 study that will be conducted in up to two cohorts.

Cohort 1 is a randomized, 2-part, crossover design. Part 1 has 3 periods, Periods 1and 2 are double blind, sponsor open, placebo controlled crossover design to evaluate the safety and tolerability and PK of the planned 400 mg and 200 mg of sisunatovir given Q12 hours x 4 days plus 1 dose as 50 mg capsules in a fed state. Period 3, is an open label period to evaluate the food effect of the planned 400 mg of sisunatovir given Q12 hours x 4 days plus 1 dose in a fasted state. Part 2, Periods 4 7, is open label to assess the palatability of 50 mg of sisunatovir in 4 different vehicles (water, infant formula, apple juice, and saline) in a randomized crossover design.

Cohort 1 will include approximately 12 participants that will be randomized into 4 sequences with 3 participants in each sequence. Each sequence will receive treatment in a pre-specified manner (see Figure 1).

Over the first 2 periods, all participants are planned to receive (A) 400 mg and either (B) 200 mg plus matching placebo or (C) placebo dosed Q12 hours for 4 days plus 1 dose in the fed state. All participants in Period 3 will receive (D) 400 mg dosed Q12 hours for 4 days

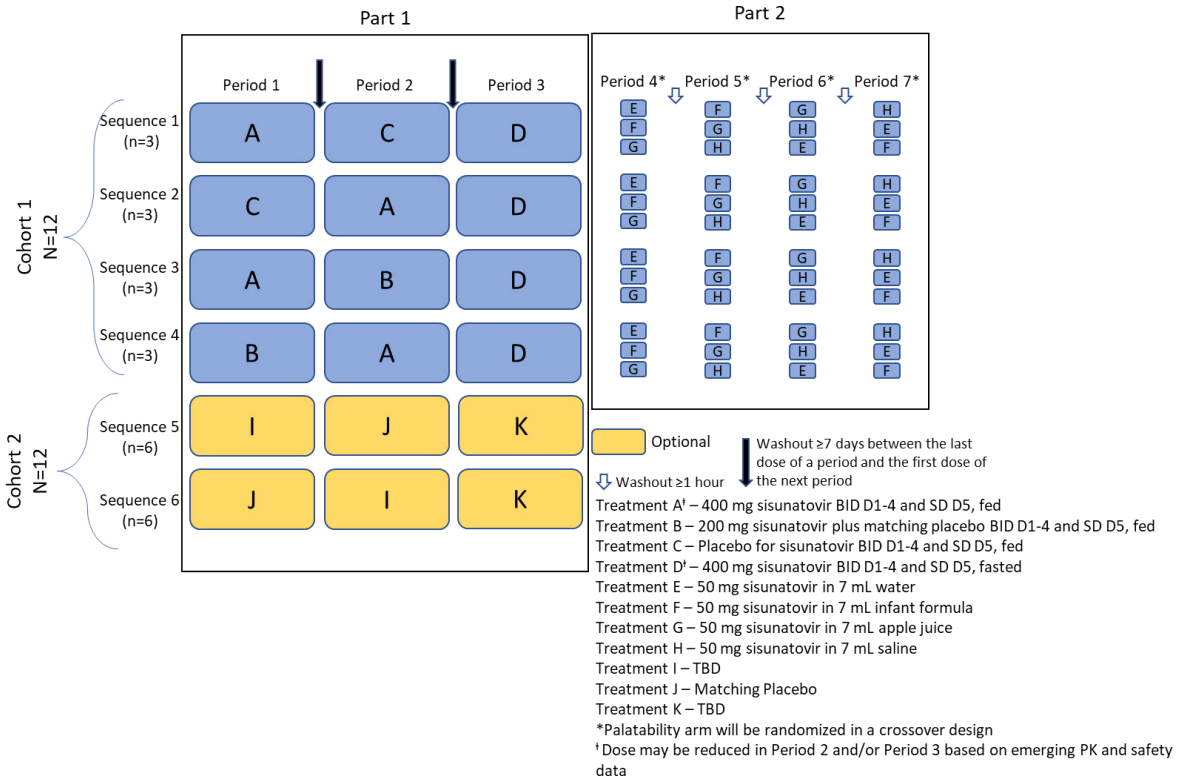
plus 1 dose in the fasted state. A minimum 7-day washout period will occur between the last dose of Periods 1 and 2 and the first dose of Periods 2 and 3.

Prior to proceeding to Period 2 of Cohort 1, the Period 1 Day 5 PK up to 12 hours post-dose will be assessed. If the mean exposures (AUC or Cmax) at 400 mg in Period 1 exceeds the rat (most sensitive species) NOAEL, the doses for the subsequent period(s) will be capped to a dose that is not expected to exceed the rat NOAEL. Similarly, prior to proceeding to Period 3 of Cohort 1, the Periods 1 and 2 Day 5 PK up to 12 hours post-dose will be assessed, and if the mean exposures (AUC or Cmax) at 400 mg exceeds the rat (most sensitive species) NOAEL, the doses for the subsequent period(s) will be capped to a dose that is not expected to exceed the rat NOAEL. Furthermore, safety will also be assessed following each period and doses for subsequent periods may be reduced if the safety and tolerability of the previous dose was not deemed sufficiently tolerated.

During Periods 4-7 participants will taste sisunatovir 50 mg capsule content in different dosing vehicles ((E) water, (F) infant formula, (G) apple juice, and (H) saline) in a cross over manner and then spit out the drug with the intention of assessing the palatability of sisunatovir in different dosing vehicles. The palatability questionnaire will be completed for each vehicle, the questionnaire asks participants to assess each vehicle at 4 different time increments after tasting. At least 60 minutes will pass between tasting each vehicle. Period 4 may start after the last PK draw of Period 3.

Cohort 2 is an optional randomized, crossover cohort with 3 periods. Periods 1-2 are double blind, sponsor open, placebo controlled crossover design evaluating the safety, tolerability, and PK of sisunatovir administered Q12 hours for 4 days plus 1 dose in a fed state. Period 3, is an open label period to evaluate the food effect of sisunatovir given Q12 hours x 4 days plus 1 dose in a fasted state. Doses will not exceed 400 mg Q12 hours x 4 days plus 1 dose. Note that if the mean Day 5 exposure exceeds the rat NOAEL in Cohort 1, the dose in Cohort 2 will be capped at a dose that is not anticipated to exceed the rat NOAEL. Cohort 2 will be conducted at the discretion of the Sponsor after review of Cohort 1 data (including PK for at least periods 1 and 2), and there will be 2 sequences of 6 participants for Cohort 2.

Figure 1. Study Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

As listed in Section 2.2, the primary endpoint is related to safety/tolerability of multiple oral doses of sisunatovir and is described in Section 3.5.

3.2. Secondary Endpoints

3.2.1. PK parameters of sisunatovir

Blood samples for the PK analysis of susinatovir will be collected according to the Schedule of Activity given in the protocol.

Plasma PK parameters of sisunatovir will be derived (if data permit) *from the concentration-time data using standard noncompartmental methods of analysis as outlined in Table 2. Actual PK sampling times will be used in the derivation of sisunatovir PK parameters when available. 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 Sisunatovir PK Parameters Definitions

Parameter	***Definition***	***Method of Determination***
AUC_{tau}	*Area under the concentration-time profile from time zero to time tau (the dosing interval), where tau = 12 hours for BID dosing.*	*Linear/Log trapezoidal method.*
$AUC_{tau}(dn)$	*Dose normalized AUCtau*	*AUC_{tau}/Dose*
C_{max}	*Maximum observed plasma concentration*	*Observed directly from data*
$C_{max}(dn)$	*Dose normalized maximum plasma concentration*	*C_{max}/Dose*
T_{max}	*Time to reach C_{max}*	*Observed directly from data as time of first occurrence*
$t_{½}$	*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 loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.*
CL/F	*Apparent clearance*	*Dose/AUC_{tau}*
V_z/F^*	*Apparent volume of distribution*	*Dose/(AUC_{tau} • k_{el})*
R_{ac}	*Observed accumulation ratio for AUC*	*AUC_{tau} Day5/AUC_{tau} Day1*
$R_{ac,Cmax}$	*Observed accumulation ratio for C_{max}*	*C_{max} Day5/C_{max} Day1*

** If data permit.*

3.2.2. Food effect on the PK of sisunatovir

The test/reference ratios for AUC_{tau} and C_{max} will be derived, with Treatment A (sisunatovir the highest tolerated dose Q12 hours administered under fed condition) as the test treatment and Treatment D (sisunatovir the highest tolerated dose Q12 hours administered under fasted condition) as the reference treatment. In addition, an estimate of the difference in T_{max} between Treatments A and D will be obtained from a non-parametric method (Hodges-Lehmann estimator).

3.2.3. Palatability of sisunatovir

The data collected for palatability assessment using the sponsor-provided palatability questionnaire will be numerically derived by measuring length (using a scale with gradations of at least 0.1 cm) of the "x" marked by the participant relative to the "good trait". For palatability assessment, the data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire.

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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 will be 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

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 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 (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 participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For Periods 1 to 3, the baseline measurement is the predose measurement on Day -1 in each period. Changes from baseline will be defined as the change between the postdose and baseline measurements in each period.

3.5.3. Vital Signs

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

For Periods 1 to 3, the baseline measurement is the predose measurement on Day 1 in each period. Changes from baseline will be defined as the change between the postdose and baseline measurements in each period.

• The maximum decrease from baseline over all measurements taken post-dose for supine blood pressure.

• The maximum increase from baseline over all measurements taken post-dose for supine pulse rate.

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 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.

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.
If 3 of more participants have an unplanned measurements at the same timepoint these may be summarized in addition to the planned timepoints.

3.5.4. Electrocardiograms

A 12-lead ECG will be obtained on all participants at screening. 12-lead ECGs will be recorded on all participants at times detailed in the SoA given in the protocol. Triplicate measurements will be performed.

The QT, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time. The average of the triplicate readings collected (where applicable) at each assessment time will be calculated for each ECG parameter. If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

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

For Periods 1 to 3, the baseline value is the average of the triplicate ECG measurements collected before dose administration on Day 1 in each period. Changes from baseline will be defined as the change between the average of the postdose triplicate ECG measurements and the baseline ECG.

The following ECG endpoints will be determined:

• Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex.

• The maximum absolute value (post-dose) will be calculated for QTcF, PR and QRS.

• The maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF.

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.

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***
Enrolled	*"Enrolled" means a participant, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization 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*

Participant Analysis Set	*Description*
	the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety Analysis Set	*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.*
PK Concentration Population	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value can be reported.*
PK Parameter Analysis Population	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest can be reported.*

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.

5.2.1. Analyses for Binary/Categorical Endpoints

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.

5.2.2. Analyses for Continuous Endpoints

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.

Log transformed continuous variables will be presented using summary statistics: number of observations, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

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 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 (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

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

The primary endpoints are related to safety/tolerability and their analyses are described Section 6.6.

6.2. Secondary Endpoints

6.2.1. PK parameters of sisunatovir

The secondary endpoints are related to PK and are described herein.

PK parameter summaries:

The plasma sisunatovir PK parameters detailed in Section 3.2.1 will be listed and summarized descriptively by treatment in accordance with Pfizer data standards for the PK Parameter Analysis Population, as data permit. Missing values will be handled as detailed in Section 5.3.1. Each PK parameter will be summarized by treatment and will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively by Treatment and Day

Parameter	Summary Statistics
AUC_{tau}, $AUC_{tau}(dn)$, C_{max}, $C_{max}(dn)$, CL/F^a, V_z/F^a, R_{ac}^a, $R_{ac,\,Cmax}^a$	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}	N, median, minimum, maximum
$t_{½}^a$	N, arithmetic mean, median, SD, %CV, minimum, maximum

a. Applicable for Day 5 only

To assess the relationship between the PK parameters and dose, dose normalized C_{max}, AUC_{tau} of sisunatovir will be plotted against dose (using a logarithmic scale), and will include individual participant values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented.

All dose normalized parameters will be listed along with other individual PK parameters.

Box and whisker plots for individual participant parameters (AUC_{tau} and C_{max}) will be presented by treatment and overlaid with geometric means. These plots may be presented for both the dose-normalized and non dose-normalized versions of these parameters, as data permit.

PK concentration summaries:

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

Presentations for sisunatovir plasma concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment, and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be provided in a separate listing.

- A summary of concentrations by treatment 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 treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

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

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

6.2.2. Food effect on the PK of sisunatovir

For the food effect evaluation, natural log transformed AUC_{tau}, and C_{max} of sisunatovir will be analyzed using a mixed effect model with sequence, and treatment as fixed effects and participant within sequence as a random effect. The Kenward-Roger adjustment for the degrees of freedom will be used. *Estimates of the adjusted mean differences (Test Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of*

adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment D (sisunatovir the highest tolerated dose *Q12 hours administered under fasted condition) is the Reference treatment and Treatment A (sisunatovir* the highest tolerated dose *Q12 hours administered under fed condition) is the Test treatment. For the food effect comparison only the data from treatment A and D will be included in the model.*

For AUC_{tau} and C_{max} a listing of the individual participant ratios (Treatment A (fed)/Treatment D (fasted)) will be provided. Box and whisker plots for individual participant parameters (AUC_{tau} and C_{max}) will be presented by treatment and overlaid with geometric means.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the CSR. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be provided in the clinical study report.

6.2.3. Palatability of sisunatovir

The sensory attributes (mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking) from the taste questionnaires (for questionnaire tool please see protocol) will be listed and descriptively summarized by treatment sequence, and question across participants. Summary statistics (mean and 90% CI) will be calculated for the various questions. Radar plots for each of 4 time points, summarizing all attributes will be generated. Boxplots of each attribute will be plotted against the time points.

Palatability of sisunatovir may be analyzed using a mixed effect model with treatment and period as fixed effects and participant as a random effect(data permitting). Estimates and corresponding 90% CIs will be obtained from the model.

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Parameter	Summary Statistics
AUC_{tau} T_{max} C_{max}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

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- a listing of all concentrations sorted by participant ID, treatment, matrix 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 treatment and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- individual concentration-time plots by treatment (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).
- median concentrations-time plots (on both linear and semi-log scales) against nominal time post-dose by treatment (all treatment on the same plot per scale, based on the summary of concentrations by dose and time post-dose).
- mean concentrations-time plots (on both linear and semi-log scales) against nominal time post-dose by treatment (all treatment on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

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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.

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 will be summarized for enrolled population in accordance with with the sponsor reporting standards.

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 treatment. 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. Concomitant Medications and Nondrug Treatments

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

6.6.1. Adverse Events

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

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.6.2. Laboratory Data

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

6.6.3. Vital Signs

Vital signs data will be listed and summarized by treatment in accordance with the sponsor reporting standards.

Absolute values and changes from baseline in supine systolic 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 3.5.3.

Mean changes from baseline for supine systolic blood pressure and pulse rate will be plotted against time post-dose. Each part will have its own output with 1 line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum decrease from baseline for supine systolic blood pressures and maximum increase from baseline for supine pulse rate will be summarized by treatment, according to sponsor reporting standards.

Minimum and/or maximum absolute values and changes from baseline for supine vital signs 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.

6.6.4. Electrocardiograms

Changes from baseline for the ECG parameters HR, QTcF , PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	***Mild (ms)***	***Moderate (ms)***	***Severe (ms)***
Absolute value	*>450-480*	*>480-500*	*>500*
Increase from baseline		*>30 and ≤ 60*	*>60*

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms.

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

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time postdose. Each period will have its own output with 1 line for each treatment. 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 of sisunatovir and fed condition. 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.

Maximum increase from baseline for QTcF will be summarized by treatment, according to sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1 (for QTcF these correspond to the Pfizer Guidance in Section 8). Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose time points will be counted in these categorical summaries.

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

7. INTERIM ANALYSES

No 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, facilitating PK/PD modeling, and/or supporting clinical development.

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7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Available safety and PK data will be reviewed after Period 1 and Period 2.

8. REFERENCES

Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018

APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

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
Supine pulse rate (bpm)	min. <40	max. >120

Appendix 2. Summary of Analyses

Endpoint	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Method
Ratio of AUC_{tau}, C_{max}	PK Parameter Analysis Population	Observed data	Mixed effect ANOVA model
PK parameters	PK Parameter Analysis Population	Observed data	Descriptive statistics
PK concentrations	PK Concentration Population	Observed and imputed (Section 5.3.1) data	Descriptive statistics
Safety Data	Safety analysis set	Observed and imputed (Section 5.3.2) data	Descriptive statistics
CCI [redacted]	[redacted]		[redacted]

Appendix 3. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
$Ae_{(0-12)}$	Amount of endogenous CCI recovered unchanged in urine from 0 to 12 hours post-dose
AUC_{tau}	area under the concentration-time profile from time zero to time tau (the dosing interval), where tau = 12 hours for BID dosing
AUC_{tau}(dn)	dose normalized AUC_{tau}
BID	twice-daily dosing
BLQ	below the limit of quantitation
BP	blood pressure
CI	confidence interval
CL/F	apparent clearance
CL_r	Renal clearance
C_{max}	maximum observed plasma concentration
C_{max}(dn)	dose normalized maximum plasma concentration
CCI	[redacted]
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
HR	heart rate
CCI	[redacted]
k_{el}	elimination rate constant estimated from the log-linear regression analysis
LLQ	lower limit of quantitation
mg	milligram
ms	milliseconds
N/A	not applicable
NC	not calculated
ND	not done
CCI	[redacted]
NS	no sample
OATP	organic anion transporting polypeptide
PK	pharmacokinetic(s)
PR	pulse rate
Q12	every 12
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT interval
QTcF	corrected QT (Fridericia method)
R_{ac}	observed accumulation ratio for AUC
$R_{ac, Cmax}$	observed accumulation ratio for C_{max}

Abbreviation	Term
RR	respiratory rate
RSV	respiratory syncytial virus
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{1/2}$	terminal plasma elimination half-life
TBD	to be determined
TEAE	treatment emergent adverse event
T_{max}	time to reach C_{max}
V_z/F	apparent volume of distribution