Protocol C5241014

A RANDOMIZED, PHASE 1, SINGLE-BLIND, MULTI-PERIOD STUDY TO INVESTIGATE THE PALATABILITY OF PF-07923568 ORAL SUSPENSION IN DIFFERENT LIQUID VEHICLES IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: 1

Date: 15 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 15 Aug 2023	Original 19 May 2023	N/A	N/A

2. INTRODUCTION

The purpose of this study is to perform palatability assessments to aid in the development of pediatric formulations of sisunatovir (PF-07923568).

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5241014. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analyses will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

N/A

2.2. Study Objectives, Endpoints, and Estimands

There are no estimands for this study.

Type	Objective	Endpoint
Primary:		
Other	• *To assess the palatability attributes of sisunatovir in different formulations*	• *Palatability Assessment Questionnaire Scoring Metrics: mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking*
Secondary:		
Safety	• *To assess safety and tolerability following oral administration of each sisunatovir formulations*	• *Assessment of TEAEs, clinical laboratory abnormalities and vital signs*

2.3. Study Design

This is a single-blind, randomized, multi-period study in healthy male and/or female adult participants. Approximately 12 participants will assess the palatability attributes of a total of

6 formulations (Formulations A to F) over 2 days in a crossover manner. There will be a maximum of 4 periods each day, and one formulation will be administered at each period for tasting in a blinding fashion, except on Day 2 where there will be one period with no administration. A minimum of 3 participants from each gender is required.

All participants will be discharged on Day 2 after completion of all required assessments. If the participant accidentally ingests the taste sample containing the active ingredient, he/she will not be permitted to continue evaluating any further taste samples and will be withdrawn from the study.

Participants who discontinue from the study may be replaced at the sponsor's discretion. The replacement participant will receive the same treatment sequences as the participant who discontinued.

The study sample dosing scheme is shown below in Figure 1.

Figure 1. Sample Dosing Scheme

	Session 1 (Day 1)				Session 2 (Day 2)			
	Period 1	**Period 2**	**Period 3**	**Period 4**	**Period 5**	**Period 6**	**Period 7**	**Period 8**
N=3	A	B	D	C	A	E	No	F
N=3	B	C	A	D	E	F	A	No
N=3	C	D	B	A	F	No	E	A
N=3	D	A	C	B	No	A	F	E

Treatment A: CCI *mg/mL Sisunatovir* CCI [redacted]
Treatment B: CCI *mg/mL Sisunatovir,* CCI [redacted]
Treatment C: CCI
Treatment D: CCI *mg/mL Sisunatovir and* CCI [redacted]
Treatment E: CCI *mg/mL Sisunatovir and* CCI [redacted]
Treatment F: CCI *mg/mL Sisunatovir,* CCI [redacted]
No: No administration and indicated as 'X' in randomization
Note CCI [redacted]

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Palatability Assessment Questionnaire Scoring Metrics: mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking

Participants will swirl the sample in the mouth for approximately 10 seconds, and then spit it out. Participants will assess various aspects of the taste, including mouth feel, bitterness, sweetness, sourness, saltiess, tongue/mouth burn, and overall liking using the Oral Solution or Suspension Palatability Questionnair (Appendix 2).

Palatiablity assessments will be carried at approximately 1 minute, 5 minutes, 10 minutes, and 20 minutes after dosing.

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.

3.2. Secondary Endpoint(s)

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

3.3. Other Endpoint(s)

N/A

3.4. Baseline Variables

N/A

3.5. Safety Endpoints

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

- Adverse events (AE)
- Clinical laboratory assessments
- Vital signs
- Electrocardiograms

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment-emergent adverse events (TEAE). If an AE starts on the same day as the first dose date, it will be considered treatment-emergent uness the CRF data indicates otherwise via explicitly recording time for AE omset which has 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 treatments 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.

A 3-tier approach for summarizing adverse events (AEs) will not be used due to the low number of participants planned to be recruited.

3.5.2. Clinical Laboratory Assessments

Clinical laboratory assessments 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, the measurement on Day -1, is within or outside the laboratory reference range for the particular laboratory parameter.

3.5.3. Vital Signs

Blood pressure and pulse rate will be measured as described 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 measurement on Day 2 and the baseline measurement.

3.5.4. Electrocardiograms

Single 12-lead ECGs will be performed as described in the protocol. The HR, PR, QT, QTcF, and QRS intervals will be captured.

The baseline measurement is the predose measurement on Day 1. Changes from baseline will be defined as the change between the postdose measurement on Day 2 and the baseline measurement. Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be determined.

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.

Population	Description	Applicable Analysis
Enrolled	*"Enrolled" means a participant'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 the study, are not considered enrolled, unless otherwise specified by the protocol.*	
Evaluable analysis set	*All participants who take at least 1 dose of study intervention and provide at least 1 corresponding assessment to the Palatability Questionnaire.*	Primary Endpoint
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.*	Secondary Endpoint

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

Descriptive analyses will be performed, and some measures will be summarized using graphical representations

The analyses related to the primary and secondary endpoints will be based on the appropriate population for analysis (see Section 4).

Unless otherwise stated, all summaries and plots will be presented by treatment group. The following treatment group labels (or similar) will be used:

- Treatment A: CCI mg/mL Sisunatovir CCI [redacted]

- Treatment B: CCI mg/mL Sisunatovir, CCI
- Treatment C: CCI
- Treatment D: CCI mg/mL Sisunatovir and CCI
- Treatment E: CCI mg/mL Sisunatovir and CCI
- Treatment F: CCI mg/mL Sisunatovir, CCI

5.2.1. Analyses for Continuous Endpoints

For continuous variables; the data will be summarized using number of participants, arithmetic mean, standard deviation (SD), median and range (minimum and maximum) in accordance with the sponsor reporting standards.

5.2.2. Analyses for Binary/Categorical Endpoints

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

5.3. Methods to Manage Missing Data

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

6. ANALYSES AND SUMMARIES.

6.1. Primary Endpoint(s)

The sensory attributes (mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking) from the palatability questionnaires (Appendix 2) will be listed and descriptively summarized by session, time point, and treatment, if appropriate. 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. Any additional feedback data as collected by the palatability questionnaire will be listed.

6.1.1. Sensitivity/Supplementary Analysis

If the data permits, palatability of sisunatovir may be analyzed using a mixed effects model. Data from multiple time ponts will be combined to be treated as the response. Treatment, sequence, timepoint, and period will be fixed effects; and participant within sequence will be a random effect. Estimates and corresponding 90% CIs will be obtained from the model.

6.2. Secondary Endpoint(s)

The secondary endpoints are related to safety/tolerability and their analyses are described in Section 6.5.

6.3. Subset Analyses

There are no planned subset analyses.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Demographic Summaries

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

6.4.2. 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 overall and treatment. Data will be reported in accordance with the sponsor reporting standards.

6.4.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.4.4. 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.

6.5. 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.

6.5.1. 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, where appropriate. Data will be reported in accordance with the sponsor reporting standards.

6.5.2. Clincal Laboratory Assessments

Laboratory data will be summarized by nominal timepoint in accordance with the sponsor reporting standards. Changes from baseline will be reported. Baseline is as defined in Section 3.5.2.

6.5.3. Vital Signs

Vital signs data will be summarized by nominal timepoint in accordance with the sponsor reporting standards. Changes from baseline will be reported. Baseline is as defined as in Section 3.5.3.

6.5.4. Electrocardiograms

ECG data will be summarized by nominal timepoint in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.5.4. Changes from baseline for the ECG parameters HR, QTcF , PR interval, and QRS complex will summarized using sponsor reporting standards. These correspond to the Pfizer Guidance[1] in Section 8.

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 in Table 2 will be tabulated.

Table 2. Categorical Classes for ECGs of Potential Clinical Concern

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

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be listed using sponsor reporting standards.

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

7. INTERIM ANALYSES

No interim analysis will be conducted for this study.

8. REFERENCES

1. 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. List of Abbreviations

Abbreviation	Term
AE	adverse event
CI	confidence interval
ECG	electrocardiogram
HR	heart rate
mg	milligram
mL	millilitre
N/A	not applicable
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
TEAE	treatment-emergent adverse event

Appendix 2. Oral Solution or Suspension Palatability Questionnaire

1. Questionnaire should be administered to adult participants, preferably by a nurse.
2. Use **colored copy** of the Palatability Questionnaire.
3. **Do not alter (reduce or enlarge) the original size of the Palatability Questionnaire**.
4. Please collect the following background information:

Background Information

Study #/Study Site	
Period and Day	
Participant ID (Rand ID)	
Treatment	

Collect Date	
Collected By	
Entered in PIMS By	
Checked in PIMS By	
Questionnaire Fully Completed (circle one)	Yes/No

Please answer the following questions and provide a mark (X) on the color bar at approximately 1 (immediately), 5, 10 and 20 minutes after dosing. Please ensure participant has access to these descriptions when completing the questionnaire.

Q1: Mouth feel – Please tell us about the mouth feel (such as grittiness, stickiness, waxiness) of the product you tasted. Good represents normal mouth feel. Bad represents bad mouth feel.

Q2: Bitterness – Please tell us about the degree of bitterness of the product you tasted. Good represents not bitter at all. Bad represents extremely bitter.

Q3: Sweetness – Please tell us about the degree of sweet taste of the product you tasted. Good represents sweet. Bad represents not sweet at all.

Q4: Sourness – Please tell us about the degree of sour taste of the product you tasted. Good represents not sour at all. Bad represents extremely sour.

Q5: Saltiness – Please tell us about the degree of salty taste of the product you tasted. Good represents not salty at all. Bad represents extremely salty.

Q6: Tongue/mouth burn – Please tell us about the degree of tongue/mouth burn of the product you tasted. Good represents no burn at all. Bad represents extreme burn.

Q7: Overall liking – Please indicate how much you like or dislike the product you tasted. Good represents like. Bad represents dislike.

Details to assess questionnaire described below:

After the participants places the mark (X) on the color bar, the main Clinical Coordinator of the study and his back up or designee will procced follows:
① Measuring the total length of the bar on the printed questionnaire:

- Place the 30 cm study dedicated transparent ruler vertically at the top of the color bar (0 level over the green top bar) and measure the length till the end of the red bottom bar

② Measuring the placement of the "X" of the color bar of the printed questionnaire:

- Place the study dedicated transparent ruler at the top of the color bar and measure the length till the intersection point level of the "X" marked on the color bar

③ Entering data in PIMS

- Enter the the length of the whole bar (in mm) and measured distance to the point level of "X" (in mm) in PIMS according to each taste assessment undergone by each participant.
- Data will be Entered by/Checked by two different Clinical Coordinators (Main & Back up) or designee.

Example: How to provide a mark (X) on the color bar.