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

Study Intervention Number:	PF-07923568
Study Intervention Name:	Sisunatovir
US IND Number:	CCI
EudraCT Number:	2022-003426-53
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5241006
Phase:	1

Brief Title: A Study to Assess the Safety, Tolerability, Pharmacokinetics, Food Effect, and Palatability of Sisunatovir in Healthy Adult Participants

Document History

Document	Version Date
Original protocol	29 November 2022
Amendment 1	23 December 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC.

Amendment 1 (23 December 2022)

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate and clarify various protocol elements based upon FAMHP feedback.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Updated to include review of PK analysis following Periods 1 and 2 in Cohort 1 and thresholds at which doses in subsequent periods would be capped prior to dosing in subsequent periods.	To assure that NOAEL would not be exceeded (in response to FAMHP feedback).
Section 1.2 Schema	Updated to reflect the possibility of dose changes in periods 2 and 3 following PK analysis.	Response to FAMHP feedback
Section 1.3 Schedule of Activities	Added 5 hour PK and ECG timepoint to Table 2.	To better characterize Tmax and in response to FAMHP feedback
Section 2.2.2 Nonclinical Pharmacokinetics and Metabolism	Expanded descriptions of projected DDI risks for sinunatovir at the 400-mg BID dose based on EMA guidance.	To clarify DDI risk for sisunatovir and in response to FAMHP feedback
Section 4.1. Overall Design	Updated to include review of PK analysis following Periods 1 and 2 in Cohort 1 and thresholds at which doses	To assure that NOAEL would not be exceeded (

Section # and Name	Description of Change	Brief Rationale
	in subsequent periods would be capped prior to dosing in subsequent periods.	in response to FAMHP feedback).
Section 4.2. Scientific Rationale for Study Design	Added rationale for interim PK analysis after Periods 1 and 2 in Cohort 1 and criteria for capping the dose in subsequent periods if the planned doses are projected to exceed the rat NOAEL	To assure NOAEL would not be exceeded in subsequent periods and response to FAMHP feedback
Section 4.3. Justification for Dose	Clarification that doses in Cohort 2 will not be a dose that is projected to exceed the rat NOAEL based on Cohort 1 PK data	To assure NOAEL would not be exceeded in subsequent periods and response to FAMHP feedback
Section 6.6. Dose Modification	Update to allow for dose modifications in Cohort 1.	To assure NOAEL would not be exceeded in subsequent periods and response to FAMHP feedback
Section 10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI	Expansion of listed prohibited concomitant medications to include sensitive MATE1 substrates, sensitive CYP2B6 substrates, strong P-gp inhibitors, strong P-gp inducers and sensitive OCT1 substrates. Also added clarification that the sponsor will be consulted prior to the administration of any concomitant medications.	Expanded list of excluded medications inresponse to FAMHP feedback
Section 2.2.2 Nonclinical Pharmacokinetics and Metabolism	Correction of bioavailability and plasma protein binding data based on report	Clarification

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Brief Title: A Study to Assess the Safety, Tolerability, Pharmacokinetics, Food Effect, and Palatability of Sisunatovir in Healthy Adult Participants

Regulatory Agency Identification Number(s):

US IND Number:	143479
EudraCT Number:	2022-003426-53
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C5241006
Phase:	1

Rationale:

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.

Objectives and Endpoints:

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

Overall Design:

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

Cohort 1 is a randomized, 2-part, crossover cohort. Part 1 has 3 periods, Periods 1 and 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 x4 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.

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.

Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the Investigator.

Number of Participants:

Approximately 12 participants will be enrolled in Cohort 1 in the study. Approximately 12 additional participants may be enrolled in Cohort 2 in the study.

Note: "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 the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria:

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Participants aged 18 to 65 years of age, inclusive, at the time of signing of the ICD.
    - All fertile participants must agree to use a highly effective method of contraception.
2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, including blood pressure, pulse rate, standard 12-lead ECG, and laboratory tests.
3. BMI of 17.5 to 35 kg/m^2; and a total body weight >50 kg (110 lb).

Exclusion Criteria:

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

3. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

4. A positive urine drug test, confirmed by a repeat test, if deemed necessary.

5. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

6. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer interpreted- ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

7. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - GFR <60 mL/min/1.73m^2 based on CKD-EPI equation;

- AST **or** ALT level ≥1.5 x ULN;
- Gamma-GT> ULN;
- Alkaline phosphatase > ULN;
- Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Study Arms and Duration:

Study Intervention(s)			
Intervention Name	PF-07923568 (sisunatovir)	Placebo for PF-07923568 (sisunatovir)	PF-07923568 (sisunatovir) Palatability in Liquid Vehicles
Unit Dose Strength(s)	50 mg	Placebo	Content of 50 mg capsule
Dose Formulation	Capsule	capsule	Capsule content dispensed in liquid vehicles
Dosage Level(s)	Planned doses are 200 mg and 400 mg BID for 5 days in Cohort 1. Doses in Cohort 2 will not exceed 400 mg	0 mg	Planned doses are the content of a 50 mg capsule of sisunatovir, dispensed in 7 ml of the following liquid vehicles: • Water • Infant formula • Apple juice • Saline
Route of Administration	Oral	Oral	Oral/"Swirl and Spit"
Use	Experimental	Placebo	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Sisunatovir: Provided centrally by the sponsor Liquid vehicles: Provided locally by the CRU
Packaging and Labeling	The PF-07923568 50 mg capsules will be provided in bulk. CRU Staff will prepare individual doses for administration	The placebo capsules will be provided in bulk. CRU Staff will prepare individual doses for administration	The PF-07923568 50 mg capsules will be provided in bulk. CRU Staff will prepare individual doses (capsule content + liquid) for administration

Study Intervention(s)			
Current/former Name(s) or Alias(es)	Sisunatovir PF-07923568 RV521	Placebo	Sisunatovir PF-07923568 RV521 Liquid vehicles: As available locally.

Statistical Methods:

A sufficient number of participants will be screened to achieve 12 participants randomized to study intervention in Cohort 1. Approximately 12 additional participants may be enrolled in Cohort 2 in the study. The sample size is empirically selected and is not based on statistical power calculation.

Safety Analysis:

All safety analyses will be performed on the safety analysis set, which is defined as 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. AEs, ECGs, BP, pulse rate and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Pharmacokinetic Analysis:

The plasma concentrations of sisunatovir will be listed and descriptively summarized by treatment and nominal PK sampling time. PK parameters for sisunatovir will be analyzed using standard noncompartmental method of analysis. Actual PK sampling times will be used in the derivation of sisunatovir PK parameters when available, otherwise nominal times will be used. In the food effect evaluation, natural log transformed AUC_{tau} and C_{max} of sisunatovir will be analyzed using a mixed effect model with treatment and sequence as fixed effects and participant within sequence as a random effect. For the food effect evaluation, estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. 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.

Palatability Assessment:

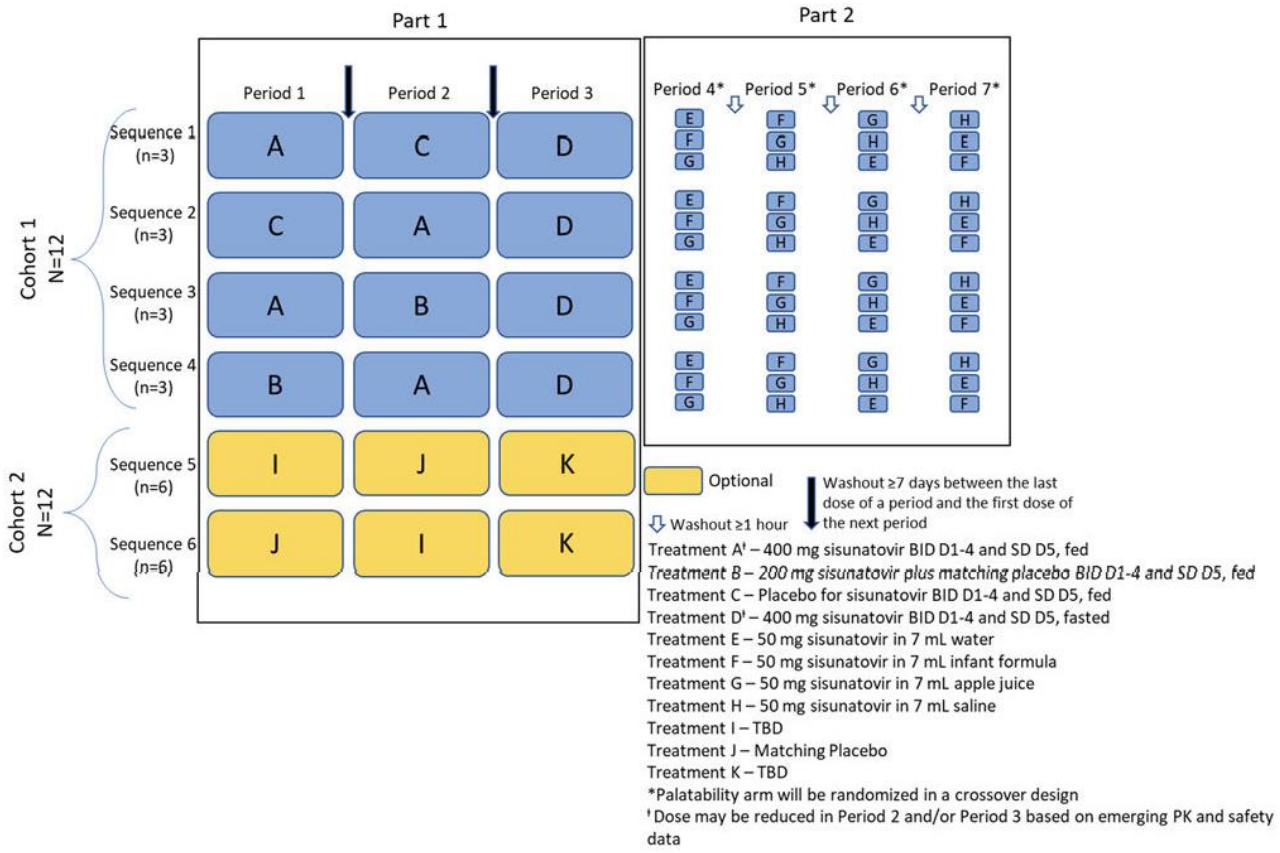
For palatability assessment, the data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire. The palatability

attributes (mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking) from the palatability questionnaires will be listed and descriptively summarized.

Ethical Considerations:

Sisunatovir is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, palatability and pharmacokinetic data for further clinical development.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed infonnation on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the paiiicipant.

Table 1. Study Schedule of Assessment

Visit Identifier· Abbreviations used in this table may be found in Annendix 11 .	**Scl'een**	**Periods 1-3**								**Periods 4-7**	**F/U 28-35 days aftel' last dose**	**ET**	**Notes**
Days Relative to Day 1 for·each period	**Day-28 to Day-2**	**Day-1**	**Dayl**	**Day2**	**Day3**	**Day4**	**Day5**	**Day6**	**Day7**	**Dayl**			• Screening '.S28 days before the first dose. • Follow-up may occur via telephone contact and 28 to 35 days after final dose. • Periods 4-7 apply only to Cohort I. • Periods 4-7 of Cohort **1** will occur on Day 7 of Period 3. •
Hom·s Aftel' Dose			0	**24**	**48**								
Informed consent	**X**												Informed consent must be obtained prior to undergoing any study-specific procedures.
CRU confinement		**X**	→	→	→	→	→	→	**X**	**X**			
Inclusion/exclusion criteria	**X**	**X**											
Medical/medication historv	**X**	**X**											
Physical exam	**X**	**X**											• PE at Screening or Period 1 Day -1 only. A brief PE at other times at the discretion of the investigator. • Including height and weight at screening onlv.
Safety laboratory	**X**	**X**		**X**	**X**		**X**					**X**	Participants should fast for at least 4 how-s before safety labs are drawn. • Includes minalysis.

Table 1. Study Schedule of Assessment

Visit Identifier· Abbreviations used in this table may be found in Aooendix **11** .	**Scl'een**	**Periods 1-3**								**Periods 4-7**	**F/U 28-35 days aftel' last dose**	**ET**	**Notes**
Days Relative to Day 1 for·each period	**Day-28 to Day-2**	**Day-1**	**Dayl**	**Day2**	**Day3**	**Day4**	**Day5**	**Day6**	**Day7**	**Dayl**			• Screening gg days before the first dose. • Follow-up may occur via telephone contact and 28 to 35 days after final dose. • Periods 4-7 apply only to Cohort I. • Periods 4-7 of Cohort I will occur on Day 7 of Period 3.
Hom·s Aftel' Dose			0	**24**	**48**								
Demo,mmhv	X												
Pregnancy test (WOCBP only)	X	X										X	• ET pregnancy testing only if participant withdraws while not admitted to the CRU.
Contraception check	X	X							**X**		**X**	**X**	Contraception check will occtu· with dischar,ze activities at the end of Period 7.
FSH (post-menopausal women only)	**X**												
Urine drug testing	**X**	**X**											
12-Lead ECG *(triplicate)*	**X**		**X**				**X**	**X**	**X**			**X**	• Single ECG for Screening. • Pre-dose ECGs are triplicate of triplicates at 30 min, 20 min, and IO min before the pre-dose meal in Periods I and 2, and 30 min, 20 min, and IO min pre-dose in Period 3. **All** other ECGs are triplicate. • DI and D5 schedule in Table 2.
Blood pressm·e and pulse rate	**X**		**X**				**X**	**X**				**X**	DI and D5 schedule in Table 2.
HIV, HBsAg, HBsAb, HBcAbHCVAb	**X**												
COVID-19 related orocedm·es	**X**	**X**	➔	➔	➔	➔	➔	➔	**X**	**X**		**X**	• Performed per local procedm·es.

Table 1. Study Schedule of Assessment

Visit Identifier· Abbreviations used in this table may be found in Aooendix **11** .	**Scl'een**	**Periods 1-3**								**Periods 4-7**	**F/U 28-35 days aftel' last dose**	**ET**	**Notes**
Days Relative to Day 1 for·each period	**Day-28 to Day-2**	**Day-1**	**Dayl**	**Day2**	**Day3**	**Day4**	**Day5**	**Day6**	**Day7**	**Dayl**			• Screening gg days before the first dose. • Follow-up may occur via telephone contact and 28 to 35 days after final dose. • Periods 4-7 apply only to Cohort I. • Periods 4-7 of Cohort **1** will occur on Day 7 of Period 3.
Hom·s Aftel' Dose			0	**24**	**48**								
Study intervention administration			**X**	**X**	**X**	**X**	**X**			**X**			• For Periods 1-3: Ql2 hours on Days 1-4; on Day *5* only the moming dose of study dmg will be administered. • The washout between last dose in previous period ?.7 days (Periods 2 and 3 only). • Periods 1 and 2 are dosed in the fed state and Period 3 is dosed in the fasted state.
Palatability Assessments										**X**			Palatability assessments will be completed at 1 min (immediately following dose), *5* min, IOmin, and 20 min after tasting dose in vehicle. • There is an at least 60 minutewashout between tasting each dose in vehicle.
Pharmacokinetic blood sampling			**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**	D2, D3, and D4 PK samples to be drawn before AM dosing. DI and D5 **PK** schedule in Table 2.
Retained Research Sample for Genetics (Prep DI)			**X**										Prep DI Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a pa1ticipant visit. • To be collected dming Period I onlv.

Table 1. Study Schedule of Assessment

Visit Identifier· Abbreviations used in this table may be found in A endix 11.	Scl'een	Periods 1-3								Periods 4-7	F/U 28-35 days aftel' last dose	ET	Notes
Days Relative to Day 1 for·each period	**Day -28 to Day-2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	Day 7	**Day 1**			• Screening 28 days before the first dose. • Follow-up may occur via telephone contact and 28 to 35 days after final dose. • Periods 4-7 apply only to Cohort I. • Periods 4-7 of Cohort I will occur on Day 7 of Period 3.
Hom·s Aftel' Dose			0	**24**	**48**								
CCI [redacted]													[redacted]
CCI [redacted]													
CRU discharge									X	X			• Participants will discharge from the unit on Day 7 of Periods I and 2. • After the last PK draw for Period 3 participants will immediately sta1t Period 4. • Participants will discharge from Period 7 after completing the final palatability assessment.
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	X	X	• See Se-ction 8.4.3 for follow-up AE and SAE assessments.

Table 2. Periods 1-3 PK Days

Visit Identifier		**For Periods 1-3 only**												**Notes**
Study Day		**Day 1 and Day 5**									**6**		**7**	
Hours After Morning Dose	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	Hour 0 = predose sample collection
Study intervention administration	X								X					• H12 dose should be given 12 hours ±1 hour after H0 dose. • On D5 only the H0 dose will be given.
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	• H12 PK draw on D1 should be completed prior to evening dosing. • H16 sample day 5 only.
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]					
Triplicate ECGs	X	X	X	X	X	X	X	X	X		X	X	X	• Pre-dose ECGs are triplicate of triplicates at 30 min, 20 min, and 10 min before the pre-dose meal in Periods 1 and 2, and 30 min, 20 min, and 10 min pre-dose in Period 3. • All other ECGs are triplicate.
Vitals	X				X			X			X			

2. INTRODUCTION

Sisunatovir 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. Sisunatovir (formerly RV521) is an inhibitor of RSV fusion (F) protein mediated fusion that is currently being investigated for the treatment of RSV infection.

2.1. Study Rationale

The purpose of the study is to assess the safety, tolerability, and PK of multiple oral doses of sisunatovir when administered with food or fasting. Palatability assessments will be conducted to aid in the development of pediatric formulations of sisunatovir.

2.2. Background

RSV, a member of the Pneumovirus family, is a significant pathogen of the very young, immunocompromised, and the elderly. RSV is ubiquitous and is known to infect almost all children by 2 years of age.[1] The clinical manifestation of RSV infection is typically mild upper respiratory tract illness. However, in infants, young children, the immunocompromised and the elderly, it can cause serious LRTI. Infants <6 months of age are at the highest risk of severe RSV infection which can lead to hospitalization, ICU admission and even death.[2,3,4]

The current management of RSV infection includes a combination of preventative and limited treatment measures, primarily consisting of supportive care. Ribavirin, a nucleoside analogue, is currently the only licensed antiviral for the treatment of RSV in children (Virazole®).[5] There is no approved antiviral for the treatment of RSV in other age groups. Most current guidelines make either no recommendation or do not recommend routine use of ribavirin due to its weak antiviral capacity, inherent toxicity and teratogenic potential.[6] Thus, a placebo controlled design is considered appropriate for trials of new antiviral agents for the treatment of RSV. Palivizumab (Synagis®) is a prophylactic monoclonal antibody that has been shown to protect infants against RSV disease and is used in specified high risk infant groups. Despite the availability of these agents, their limited use means that treatment of RSV infection remains an area of unmet need.

Sisunatovir is a potent inhibitor of RSV F protein mediated cell-to-cell fusion. The RSV F protein is essential for the entry of the virus to the host cell. Cell surface expression of the F protein also causes cell-to-cell fusion, leading to the giant syncytia characteristic of RSV infection.

The sisunatovir preclinical profile, as well as the safety and tolerability data from the first human dosing studies, provide a strong rationale for the clinical development of sisunatovir.

2.2.1. Nonclinical Pharmacology

- *In vitro*, sisunatovir has demonstrated potent inhibition of RSV F protein-mediated cell-cell fusion, and of infection by a panel of RSV laboratory and clinical isolates of both A and B strains in the RSV plaque assay. Sisunatovir treatment resulted in a significant reduction in RSV infection in a human airway epithelial cell model.

- *In vivo*, sisunatovir resulted in a marked reduction in lung virus titer in a Balb/C mouse model of RSV infection.

- An *in vitro* secondary pharmacology study did not reveal any significant off-target activity for sisunatovir.

- Refer to the sisunatovir IB for further details.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

- In animal pharmacokinetic studies sisunatovir showed slow oral absorption, moderate-high CL, high volume of distribution, and oral bioavailability of 46%, 42-132%, and 44% in mouse, rat, and dog, respectively.

- Plasma protein binding of sisunatovir was low to moderate across species, with average fraction unbound of 67%, 38%, 52%, 27%, and 48% in human, mouse, rat, dog and guinea pig, respectively. Repeat dosing studies in the rat show that extensive distribution of sisunatovir to the lungs occurs, resulting in high lung to plasma ratio. This effect is greater than dose proportional from 50 mg/kg to 150 mg/kg.

- Consistent with the results of the midazolam DDI study (C5421004), *in vitro* studies indicate that CYP3A4 is the main CYP isoform that metabolizes sisunatovir with minor contribution from CYPs 2C9 and 2D6.

- Based on EMA guidance, *in vitro* studies indicate a DDI risk exists for OATP1B1/1B3, OCT1, MATE1, OCT2, and OAT3. However, ratios of unbound hepatic inlet concentrations relative to Ki values are low, and DDI risk is considered unlikely for OATPs, OCT2, and OAT3. The pharmacokinetics of OCT1 and MATE1 substrates may be altered when co-administered with sisunatovir, and therefore sensitive OCT1 and MATE1 substrates are prohibited in this protocol (Appendix 9).

- Based on calculations from EMA guidance *in vitro* studies indicate there is a risk of inhibition of CYPs 1A2, 2B6, 2C9, 2C19, and 3A4. The DDI with CYPs 1A2, 2C9, and 2C19 is predicted to be minimal (predicted less than 25% increase in AUC of a sensitive substrate) and DDI with CYP2B6 is predicted to be weak. A DDI study conducted with sisunatovir (200 mg BID) and midazolam as a sensitive CYP3A4 probe substrate (C5241004) indicate that sisunatovir is a moderate 3A4 inhibitor. There is also a possibility that the pharmacokinetics of CYP2B6 substrates may be altered when coadministered with sisunatovir. Based on these findings sensitive or narrow therapeutic index 3A4 substrates and narrow TI CYP2B6 substrates are prohibited in this protocol (Appendix 9) .

- *In vitro* studies indicate that sisunatovir is a Pgp substrate; therefore, co-administration of inhibitors for the transporter (P-gp) may result in increased exposure to sisunatovir (approximately 2-fold). 'A clinical DDI study (C5241004) indicated that verapamil (a P-gp and CYP3A4 inhibitor) coadministration produced

an approximately 2.5-fold increase in exposure to sisunatovir. Based on these findings, strong inhibitors or inducers are prohibited in this protocol (Appendix 9).

- The major metabolites produced in all species appeared to be hydroxylated metabolites although some Phase 2 metabolites were also detected in all species. The in vitro metabolite profile in the rat, mouse, dog, guinea pig, and human were similar with the exception of M4, an apparent double hydroxylation only apparent in human at low levels.

2.2.3. Nonclinical Safety

- In the repeat dose toxicity studies in adult (up to 28 days) and neonatal/juvenile rats and dogs, the MTDs were defined by body weight loss and reduced food consumption accompanied by adverse clinical observation of varying severity. In dogs, there was dose-related incidence of emesis and liquid feces at ≥15 mg/kg/day. The key target organ for toxicity in adult animals was the hepatobiliary system, which included both degenerative and inflammatory changes in bile duct, in rats (≥60 mg/kg/day) and dogs (≥45 mg/kg/day). In dogs, the hepatobiliary findings correlated with elevated plasma levels of ALP, ALT and GGT. In addition, the findings observed only in rats were in kidney (degeneration/regeneration of medullary tubules) at ≥120 mg/kg/day, lung (vascular degeneration/necrosis) at 240 mg/kg/day (non-tolerated dose) and trachea (epithelial degeneration and subepithelial inflammation [predominantly in females]) at 120 mg/kg/day in 14 and/or 28-day studies. In the 28-day dog repeat dose toxicity study, the NOAEL was 15 mg/kg/day corresponding to C_{max} of 729 ng/mL and AUC_{tau} of 9510 ng.h/mL. In the 28-day rat repeat dose toxicity study, the NOAEL was 60 mg/kg/day corresponding to C_{max} of 322 ng/mL and AUC_{tau} of 4725 ng.h/mL.

- In the embryo-fetal toxicity studies in rat (GD6-17) and rabbit (GD6-18), there were no effects on pregnancy or embryo-fetal development. In rat, the NOAEL for maternal toxicity was 45 mg/kg/day based on the transient initial body weight loss followed by dose-related decreased body weight gain at ≥45 mg/kg/day. The NOAEL for embryo-fetal toxicity in rat was 60 mg/kg/day, corresponding to systemic maternal exposure (AUC_{24}) of 9830 ng.h/mL on Day 15 of gestation. In rabbit, maternal toxicity was limited to lower body weight gain and food intake at 45 mg/kg/day. The NOAEL for embryo-fetal development in rabbit was 45 mg/kg/day, corresponding to a systemic maternal exposure (AUC_{24}) of 220 ng.h/mL on Day 16 of gestation.

2.2.4. Clinical Overview

Table 3. Completed Sisunatovir Studies

Study Number (Status)	Study Type/Key Design Features	Study Population	Dose, Dosing Regimen	Formulation Used
C5241001 (previously REVC001[a]) (completed)	Phase 1, randomized, double blind, placebo controlled, safety, tolerability, PK, food-effect of SAD and MAD	Healthy participants	Dose range: 10 mg – 525 mg (SAD); 36 participants Dose range: 175 mg – 350 mg; BID (MAD), Food effect; 24 participants	Liquid Formulation DIC
C5241002 (previously REVC002) (completed)	Phase 2a, randomised, double blind, placebo controlled	Healthy participants inoculated with RSV CV	200 mg or 350 mg BID for a total 10 doses; 66 Participants	DIC
C5241004 (previously REVC004) (completed)	Phase 1, adaptive, part randomised, part open-label, drug interactions, safety, tolerability	Healthy participants	200 mg; BID; 62 Participants	DIC
C5241005 (previously REVC005) (completed)	Phase 1, open-label, single-dose, PK, safety, and tolerability study	Healthy participants	200 mg, 4 single doses total; 9 Participants 1 ×: DIC (fed) 1 ×: DPB (fed) 1 ×: DPB dispersed in H2O (fed) 1 ×: DPB dispersed in H2O (fasted) [wash-out: 3 days between each of the 4 dosing days]	DIC DPB

a. A total of 8 participants received the liquid dosage formulation of sisunatovir in a solution, at a concentration of 5 mg/mL, containing HBP cyclodextrin, Lycasin, flavoring agent (strawberry), benzoic acid and water) and 68 subjects received DIC in the study.

A total of 201 adult healthy participants have received sisunatovir in 4 completed clinical studies (C5241001, C5241002, C5241004 and C5241005) investigating the PK profile, effects of food on PK, effects of formulation on PK (C5241001, C5241005), DDIs (C5241004), and the efficacy in an RSV Viral Challenge Study (C5241002) at doses ranging from 10 mg to 525 mg. In addition, as of 03 October 2021, 45 pediatric patients hospitalized due to RSV LRTI have been enrolled into the ongoing C5241003 study.

The administration of sisunatovir was well tolerated at all doses, dosage forms and dosing regimens tested. In the adult healthy participants treated to date, the occurrence of TEAEs considered related to sisunatovir has been low. Most commonly reported treatment-related

TEAEs were in the GI disorders SOC; nausea, diarrhea and abdominal pain. These TEAEs have been mild to moderate in intensity and resolved without sequelae. Most events attributed to IMP involved the gastrointestinal tract with nausea, diarrhea, and abdominal pain/discomfort/distension being the most common and occurring more commonly with the 350 mg dose of sisunatovir than with the 200 mg sisunatovir dose, where the number of participants reporting these events were lower and similar to those on placebo. In children, sisunatovir is required to be suspended in a solution to enable oral administration, there has been evidence of poor tolerability when sisunatovir was suspended in water as a single dose of 2.0 mg/kg in children aged 6-36 months, resulting in expulsion of the oral dose. Suspension in breast milk, formula milk or saline appeared to improve the palatability, with all doses being successfully administered to children aged 1 to 36 months in study C5241003.

As of 28 October 2022, there have been no SAEs attributable to sisunatovir and no deaths in the clinical studies.

In adults, sisunatovir is slowly absorbed reaching maximum plasma concentrations (t_{max}) at 5-6 hours (hrs) with a relatively moderate clearance, resulting in a half-life of 7-10 hours in healthy participants. Dosing to steady state resulted in steady state concentrations being reached after approximately 2 days of dosing resulting in 2-4 fold accumulation of exposure. AUC and C_{max} values increased in a greater than dose proportional manner across single and multiple dose studies. Following 5 days of dosing, the variability in PK parameters was high, with % CV ranging from 67.4-84% for C_{max} and 71.9-144% for AUC_{12}.

The effect of food on the single dose pharmacokinetics was assessed for the DIC and DPB dispersed in water. For the DIC the extent of systemic exposure to sisunatovir (geometric mean AUC_{inf} under fed and fasted conditions) was 357 and 221 ng.h/mL respectively, with the between-subject variability being lower under fed conditions (CV 64.1% compared with 198%). The ratio of fed/fasted was 218% (90% CI 94.2 - 502%) for C_{max} and 162% (90% CI 83.0 – 316%) for $AUC_{0\text{-}inf}$. For the DPB dispersed in water the extent of systemic exposure to sisunatovir (geometric mean $AUC_{0\text{-}\infty}$) under fed and fasted conditions was 371 and 337 ng.h/mL respectively, with the between-subject variability being slightly lower under fasted conditions (CV 49.0% compared with 61.6%). The ratio of fed/fasted was 107.7% (90% CI 78.0 – 148.8%) for C_{max} and 110.0% (90% CI 85.6 – 141.4%) for $AUC_{0\text{-}inf}$. Inter-individual variability as illustrated by the %CV geometric mean suggests this was greater following administration of DPB in the fed state.

Clinical DDI Study C5241004 demonstrated that the disposition of sisunatovir is expected to be affected by moderate to strong inhibitors and inducers of CYP3A4. Furthermore, sisunatovir was demonstrated to be a moderate inhibitor of CYP3A4, so dose adjustments for compounds that are sensitive substrates for CYP3A4 may need to be considered.

In an RSV challenge study, sisunatovir treatment resulted in a statistically significant reduction in AUC of RSV viral load compared with placebo; 55.25% (p=0.007) and 63.05% (p=0.002) for the 200 mg and 350 mg sisunatovir dose groups respectively (dosed Q12 hours for 5 days). Results for the AUC of total symptom score were consistent with the

viral load AUC. Geometric mean AUCs of total symptom score were 195.56, 30.79 and 31.76 hours x score for placebo, 200 mg sisunatovir and 350 mg sisunatovir, respectively. The reduction in AUCs of total symptom score compared with placebo was statistically significant for both sisunatovir treatment groups; p=0.009 (70.84%) and p=0.002 (74.42%), (Wilcoxon Rank-Sum test) for the 200 mg and 350 mg sisunatovir dose groups, respectively.

More detailed information about results of clinical studies for sisunatovir may be found in the IB, which is the SRSD for this study.

2.3. Benefit/Risk Assessment

Sisunatovir is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

For healthy participants participating in this study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of sisunatovir as a potential new, pharmacological agent for the treatment of RSV. As of 14 September 2022, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.1. The clinical impact of these potential risks will be minimized through standard, intensive, inpatient monitoring of the participants following administration of multiple oral doses of the study intervention.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sisunatovir may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: sisunatovir		
Hepatobiliary system effects	Degenerative and inflammatory changes in the bile duct of both rats (≥60 mg/kg/day) and dogs (≥45 mg/kg/day) in studies of up to 28 days, with elevated plasma levels of ALP, ALT and GGT in dogs only. Evidence of recovery for all findings following a 14-day treatment-free period.	Standard monitoring including laboratory (ie, transaminases, ALP, GGT) and AE monitoring.
Gastrointestinal effects	Transient dose-related incidence of emesis and liquid feces in dogs at doses ≥15 mg/kg/day in studies up to 28 days. Additionally, inflammation in duodenum, gall bladder, and liver at 45 mg/kg/day noted in 28-day dog study. In previous clinical studies sisunatovir has been associated with mild GI AEs.	As this is an investigational agent, there is some risk that is mitigated by close observation of AEs, etc. Participants will be closely evaluated in an inpatient setting to monitor for GI AEs. If needed, palliative alleviating measures such care as antiemetics may be provided.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Renal effects	Degeneration/regeneration of medullary tubules was noted in rats at ≥120 mg/kg/day in studies of up to 28 days; considered non-adverse based on lack of clinical pathology changes.	Standard monitoring including laboratory and AE monitoring.
Cardiovascular effects	Myocardial degeneration and necrosis was noted at 240 mg/kg/day (non-tolerated dose) in a 14-day rat study. No similar effect in rats at 120 mg/kg/day in the 28-day study, or in dogs at any dose, for 14 or 28 days.	Monitoring will include vital signs, including heart rate, and ECG assessments.
Pulmonary effects	Vascular degeneration/necrosis in lung at 240 mg/kg/day and epithelial degeneration/necrosis in trachea at 120 mg/kg/day in 14-day rat study. No similar effect in rats at 120 mg/kg/day in the 28-day study, or in dogs at any dose, for 14 or 28 days. Phase 1 FIH study (C5241001) showed no adverse clinically significant changes in safety laboratory parameters (including troponin), ECGs and vital signs.	There will be standard safety monitoring including vital signs and of adverse events.
Thymus effects	Lymphoid atrophy and decreased thymus weight and reduced size of thymus in both rats (≥120 mg/kg/day) and dogs ≥15 mg/kg/day) in studies of up to 28 days. Evidence of recovery following a 14-day treatment-free period. These findings are secondary to stress and not directly sisunatovir related	Standard monitoring including laboratory (ie, complete blood count with differential) and AE monitoring. Brief 5-day course regimen should further limit this potential risk.
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments according to the Schedule of Activities.

2.3.2. Benefit Assessment

For healthy participants participating in this study, no clinical benefit is expected.

2.3.3. Overall Benefit/Risk Conclusion

Sisunatovir is not expected to provide any clinical benefit to healthy participants in this study.

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with sisunatovir are justified by the anticipated benefits that may be afforded to participants with RSV.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
P1imary:	**Primary:**
• To characterize the safety and tolerability of multiple oral doses of sisunatovir in healthy adult participants	• Assessment ofTEAEs, clinical laboratory abnonualities, vital signs, and 12-lead ECGs
Secondary:	Secondary:
• To characterize the PK of multiple oral doses of sisunatovir	• PK Parameters AUCtau, Cmax., Tmax, AUCtau(dn), Cmax(dn) for Day 1 and AUCtau, Cmax, Tmax, AUCtau(dn), Cmax(dn), CL/F, Rae, Rac,Cmax; and t112 and V,/F (if data penuits) post last dose on Day 5
• To evaluate the effect of food on the PK of multiple oral doses sisunatovir	• The ratio of AUCtau and Cma...,on Day 5; Tmax on Day 5
• To characterize the impact ofliquid vehicles on the palatability of sisunatovit·	• Palatability Assessment Questionnait·e Scoring Metrics: mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, overall liking
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1 study that will be conducted in up to two coho1ts.

Coho1t 1 is a randomized, 2-part, crossover design. Pait 1 has 3 periods, Periods 1 and 2 ai·e 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. Pait 2, Periods 4-7, is open label to assess the palatability of 50 mg of sisunatovir in 4 different vehicles (water, infant fo1mula, apple juice, and saline) in a randomized crossover design.

Coho1t 1 will include approximately 12 paiticipants that will be randomized into 4 sequences with 3 paiticipants in each sequence. Each sequence will receive treatment in a pre-specified manner (Section 1.2 Schema).

Paiticipants will be admitted to the CRU on Day -1 to undergo baseline procedures. Over the first 2 periods, all paiticipants ai·e 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 paiticipants in Period 3 will receive (D) 400 mg dosed Q12 hours for 4 days plus 1 dose in the fasted state. Note that the dose levels for Periods 2 and 3 ai·e dependent upon the PK in the previous periods as described below.

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.

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.

Periods 4-7 will consist of a palatability assessment where 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. For each of the palatability assessments, 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 and the projected exposure based on emerging data from Cohort 1 for the dose selected for Cohort 2 will not 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.

Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor’s discretion in collaboration with the Investigator.

4.2. Scientific Rationale for Study Design

The primary purpose of this study is to assess the safety and tolerability of 400 mg sisunatovir when dosed Q12 hours for 4 days plus 1 dose. In a clinical study evaluating the effect of sisunatovir on RSV viral load following a viral challenge in healthy participants indicated that both 200 and 350 mg Q12 for 5 days robustly decreased viral load relative to placebo (C5241002). The effect at the 350 mg dose was numerically superior to the 200 mg dose; however, the 350 mg dose was associated with GI-related AEs, which was also consistent with data from the MAD study (C5241001) indicating an increase in GI AEs at higher doses, the majority of GI-related AEs were mild. Since sisunatovir was dosed in the fasted state in these studies, it is not known if food will ameliorate these GI AEs. To fill this knowledge gap, the first 2 periods of Cohort 1 are designed to assess the safety and tolerability of 400 mg Q12 hours (n=12) versus 200 mg Q12 hours (n=6) and placebo (n=6). As a secondary objective, the effect of food on the safety, tolerability and PK of sisunatovir at the 400 mg Q12 hours dose will be compared. Thus, the data from the first 3 periods of Cohort 1 are designed to assess the highest well-tolerated dose of sisunatovir that can be assessed in future clinical studies and if food can ameliorate any potential GI AEs.

Since the projected exposure at the 400-mg dose is expected to provide approximately 1.2x margins for AUC and Cmax using the rat NAOEL as the most sensitive species, the PK from each of Period 1 and Period 2 will be assessed prior to dosing the subsequent period. If the Day 5 exposure at the 400-mg dose exceeds the rat NOAEL (most sensitive species), then the dose in subsequent periods will be capped at a dose that is not projected to exceed the rat NOAEL. Note doses in Periods 2 and 3 may be adjusted based on safety findings from the previous dosing periods (see Section 4.1).

Optional Cohort 2 is included and will only be conducted at the discretion of the sponsor after reviewing data from at least the first 2 periods of Cohort 1. This cohort could potentially be used to collect data at a lower dose (e.g., 300 mg) or collect additional data at a dose that does not exceed 400 mg Q12 hours, depending on the exposures observed in Cohort 1.

In Cohort 1 only, the palatability of sisunatovir will be assessed to aid in development of pediatric formulations. These assessments will be conducted at least 48 hours after the last dose in Period 3, to allow for collection of the final PK sample and complete assessment of and AEs associated with the multiple dosing scheme. Palatability will be assessed by all participants in 4 different vehicles with a minimum of 1 hour between each vehicle, 1 hour washout has been used for the palatability assessment of other compounds. In each case, the drug in vehicle will be swirled in the mouth and spat out since it is not necessary to consume the drug to assess palatability. API blend in Pharmacopeial grade water will be used to assess the taste of the API blend. API blend in formula milk and apple juice will inform whether food vehicles are likely to improve palatability. API blend in saline will enable understanding of whether saline reduces bitter perception and improves palatability.

The highest dose planned in this study (400 mg Q12 hours x 4 days plus 1 dose) is slightly higher than the previous highest multiple oral dose tested (350 mg Q12 hours x 5 days). For

this reason, in addition to AE monitoring, labs, vitals and ECGs will also be assessed. In order to facilitate possible PK/QTc modeling, ti·iplicate ECG measures will be taken.

As this is healthy paiiicipant study, the use of concomitant medications in this study is expected to be minimal. Nevertheless, according to the DDI risk assessment for sisunatovir as described in Section 2.2.2, sisunatovir is a moderate inhibitor of CYP3A4 and is projected to be a weak inhibitor of CYP2B6. For this reason sensitive and naiTow TI CYP3A4 subsu-ates and sensitive naiTow TI CYP2B6 substi·ates ai·e prohibited in this study. Since sisunatovir is a Pgp and CYP3A4 subsu-ate, su-ong and moderate CYP3A4 inhibitors and sti·ong Pgp inhibitors ai·e also prohibited. Lastly, due to risk ofMATEl and OCTl inhibition, sensitive substi·ates of these ti·anspo1iers ai·e prohibited.

CCI [redacted]

4.2.1. Choice of Contraception/Barrier Requirements

There is no suspicion of human teratogenicity based on the intended phaimacology of the compound. Human reproductive safety data are limited for sisunatovir, therefore the use of a highly effective method of conti·aception is required for all fe1iile paiiicipants (see Appendix 4).

4.2.2. Collection of Retained Research Samples

Retained Reseai·ch Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.2.3. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for fmiher analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

To investigate the effect of sisunatovir on clinical activity following RSV infection, a viral challenge clinical study in healthy pa1iicipants was conducted where doses of200 mg or 350 mg Q12 x 5 days were administered following inoculation of an RSV infection. In this study, at both does evaluated, sisunatovir robustly decreased viral load and alleviated RSV symptoms relative to placebo. While statistically significant differences were not observed between the two dose levels, the 350 mg dose was numerically superior to the 200 mg dose.

While these data do demonsu-ate phaimacological activity, effects in the viral challenge study have not ti·anslated to robust effects in clinical ti·ials evaluating patient populations (ie, in ti·eatment of RSV). One possible reason for this is that in the ti·eatment of RSV dmg intervention occurs several days after infection whereas the proximity of staii of ti·eatment to infection in the viral challenge study is much sooner. For this reason, it is desired to dose sisunatovir Phase 2/3 efficacy studies at doses that maximize coverage over EC90 at a safe

and well tolerated dose. Additionally, dosing at higher multiples over EC90 may confer protection against resistance.

Sisunatovir was generally well tolerated in the viral challenge study as well as other Phase 1 studies conducted to date. However, an increased incidence of GI AEs were observed at the 350 mg dose relative to the 200 mg dose. Higher rates of GI AEs were also observed at higher doses within the Phase 1 program. In these studies, sisunatovir was dosed in a fasted state. Although improved GI tolerability has been observed for some anti-infective agents when dosed with food, it is not clear if GI tolerability of sisunatovir will improve with food.

The primary purpose of Cohort 1 of this study is to evaluate the safety and tolerability of the 400 mg Q12 hours x 4 days plus one dose dosing regimen and if any potential GI AEs can be mitigated with food. Therefore, within the first 2 periods of Cohort 1, each participant will receive 400 mg Q12 hours x 4 days plus 1 dose of sisunatovir with food (compared to placebo or 200 mg Q12hours). In Period 3 of Cohort 1, participants will receive 400 mg Q12 hours x 4 days plus 1 dose fasted to directly compare PK, safety and tolerability in the same participants dosed fed at the same dose level. Note doses in Periods 2 and 3 may be adjusted based on PK and safety findings from the previous dosing periods (see Section 4.1).

The effect of food on the pharmacokinetics of sisunatovir has been variable in Phase 1 studies. However, the effect of food on the pharmacokinetics of sisunatovir using the formulation to be used in this study (dry powder blend in capsules) showed minimal food effect.

As the exposure of sisunatovir increases in a greater than dose proportional manner, the steady state exposure at the planned dose in Cohort 1 (400 mg Q12 hours) is expected to be ~40% greater than the exposure at the highest dose studied to date (350 mg Q12 hours). At this dose, the anticipated safety margin over rat (most sensitive species) NOAEL AUC and C_{max} in the 28-day toxicology study are 1.2-fold.

Cohort 2 in this study is optional and will only be conducted at the discretion of the sponsor after reviewing data from Cohort 1. The dose assessed in Cohort 2 will not exceed 400 mg Q12 hours x 5 days or a dose that is projected to exceed the rat NOAEL based on Cohort 1 PK data. This cohort may be used to assess a lower dose (e.g., 300 mg) or may be used to collect additional data at the same dose that has been tested in Cohort 1 and is viewed as safe. These data may then be used to define the dose and dosing instructions in Phase 2/3.

The dose for the palatability cohort (50 mg in a 7 mL dosing solution) was selected to be close to the anticipated drug concentration in pediatric studies.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Participants aged 18 to 65 years of age, inclusive, at the time of signing of the ICD.

    - All fertile participants must agree to use a highly effective method of contraception.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, including blood pressure, pulse rate, standard 12-lead ECG, and laboratory tests.

Other Inclusion Criteria:

3. BMI of 17.5 to 35 kg/m^2; and a total body weight >50 kg (110 lb).

4. Capable of giving signed informed consent as described in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations which includes compliance with requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or

allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

- Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).
- History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.
- Positive test result for SARS-CoV-2 infection on Day -1.

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

3. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention with the exception of moderate/strong CYP3A inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.9 for additional details).

4. Current use of any prohibited concomitant medication(s) or participant unwilling/unable to use a permitted concomitant medication(s).

5. Female participants taking hormonal contraceptives or hormone replacement therapy within 28 days of the first dose of study treatment.

- Injectable hormone therapy (eg, DepoProvera®) must be discontinued at least 6 months prior to the first dose of study treatment.

Prior/Concurrent Clinical Study Experience:

6. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

7. A positive urine drug test, confirmed by a repeat test, if deemed necessary.

8. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg

(diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

9. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

10. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - eGFR <60 mL/min/1.73m^2 based on CKD-EPI equation;
    - AST **or** ALT level ≥1.5 x ULN;
    - Gamma-GT> ULN;
    - Alkaline phosphatase > ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusion Criteria:

11. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

12. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

13. History of sensitivity to sisunatovir or any of the formulation components.

14. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.

15. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

16. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.3) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.

- On Dosing days in periods 1 and 2, participants will consume a standard meal approximately 30 minutes prior to dosing. They should be encouraged to complete their meals on Day 1 and Day 5 (PK sampling days) by approximately 10 minutes prior to anticipated dosing.

- During Period 3, lunch will be the first meal after an overnight fast of approximately 10 hours.

- During the palatability assessment periods, there will be at least 60 minutes between meals and palatability assessments.

- Lunch will be provided approximately 4 hours after dosing.
- In Period 3, dinner will be provided approximately 13 hours after AM dosing (1 hour after PM dosing).
- In Period 3, an afternoon snack may be permitted approximately 7.5 hours after AM dosing.
- An evening snack may be permitted, for all periods.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.
- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing. These criteria only apply to the AM doses on Days 1 and 5 (Periods 1-3).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and non-investigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to sisunatovir and placebo.

6.1. Intervention(s) Administered

Study Intervention(s)			
Intervention Name	PF-07923568 (sisunatovir)	Placebo for PF-07923568 (sisunatovir)	PF-07923568 (sisunatovir) Palatability in Liquid Vehicles
Unit Dose Strength(s)	50 mg	Placebo	Content of 50 mg capsule
Dose Formulation	capsule	Capsule	Capsule content dispensed in liquid vehicles
Dosage Level(s)	Planned doses are 200 mg and 400 mg BID for 4 days plus 1 dose in Cohort 1. Doses in Cohort 2 will not exceed 400 mg Q12 hours.	0 mg	Planned doses are the content of a 50 mg capsule of sisunatovir, dispensed in 7 ml of the following liquid vehicles: • Water • Infant formula • Apple juice • Saline
Route of Administration	Oral	Oral	Oral/"Swirl and Spit"
Use	Experimental	Placebo	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Sisunatovir: Provided centrally by the sponsor Liquid vehicles: Provided locally by the CRU
Packaging and Labeling	The PF-07923568 50 mg capsules will be provided in bulk. CRU Staff will prepare individual doses for administration	The placebo capsules will be provided in bulk. CRU Staff will prepare individual doses for administration	The PF-07923568 50 mg capsules will be provided in bulk. CRU Staff will prepare individual doses (capsule content + liquid) for administration

Study Intervention(s)			
Current/former Name(s) or Alias(es)	Sisunatovir PF-07923568 RV521	Placebo	Sisunatovir PF-07923568 RV521 Liquid vehicles: As available locally.

Study intervention will be supplied by Pfizer as 50-mg capsules.

Matching placebo capsules will also be provided.

Capsules will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

6.1.1.1. Period 1 and 2

During Periods 1 and 2 for Cohorts 1 and 2, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) approximately 30 minutes after the start of a standard breakfast that will be consumed over approximately 20 minutes. Participants will receive the evening dose of study intervention 12 hours after the morning dose (plus or minus 1 hour) approximately 30 minutes after the start of a standard dinner that will be consumed over approximately 20 minutes. On Day 5 in each period only the morning dose of study intervention will be administered. Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. Participants may receive additional ambient temperature water up to 100 mL, if needed. This will be documented by the site. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

6.1.1.2. Period 3

During Period 3 for Cohorts 1 and 2, participants will receive morning study intervention at approximately 0800 hours (plus or minus 2 hours). For the Day 1 morning and Day 5 morning doses, the pre-dose fasting period is 10 hours and post-dose fasting period is a minimum of 4 hours. For all Days 2, 3, and 4 morning doses, the pre-dose fasting period is 8 hours and the post-dose fasting period is a minimum of 1 hour. For evening doses, the pre-dose fasting period is 4 hours, and the post-dose fasting period is a minimum of 1 hour. On Day 5 only the morning dose of study intervention will be administered. For all doses, participants will have nothing to drink (including water) for 1 hour pre-dose and 1 hour post-dose. Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. Participants may receive additional ambient temperature water up to 100 mL, if needed. This will be documented by the site. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

On Day 1 and Day 5 for morning doses, in order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

6.1.1.3. Periods 4-7 (Cohort 1 only)

During Periods 4-7, participants will be assessing the taste of sisunatovir in a variety of vehicles using the questionnaire in Appendix 10 . Participants will taste 50 mg of sisunatovir in 7 ml of the following vehicles: water, saline, apple juice, and infant formula, given in a randomized order. Participants will swirl the study intervention in their mouth for 10 seconds and then spit it out. Participants will assess various aspects of the taste using the questionnaire in Appendix 10: Oral Solution or Suspension Palatability Questionnaire at approximately 1 minute, 5 minutes, 10 minutes, and 20 minutes after spitting. There will be at least 60 minutes between tasting each study intervention, and at least 60 minutes after meals. Participants may eat plain crackers and water to cleanse their palate between assessments.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the CRU procedures.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the CRU's procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Sisunatovir and placebo will be prepared by qualified unblinded site personnel according to the IPM. Blinded study intervention will be administered in a blinded fashion to the participant. See the IPM for instructions on how to prepare the study intervention for administration or palatability assessment. Capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist).

6.3. Assignment to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

The first 2 periods of each cohort are double blind (sponsor open) design.

Study intervention administrated in Periods 3 to 7 of the study will be open to the participant, Investigator and Sponsor or Sponsor-designate personnel responsible for study monitoring activities (including all site monitoring activities).

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention. Study intervention administrated in Periods 3 to 7 of the study will be open to participant.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention. Study intervention administrated in Periods 3 to 7 of the study will be open to Investigator and other site staff.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme.

In the first 2 periods, in order to maintain the blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation, following randomization or dispensing.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

As this is a sponsor open study, a limited number of the sponsor's team members (excluding site staff) may conduct unblinded reviews of the data during the course of the study for the purpose of safety and tolerability assessment, facilitating PK/PD modeling, and/or supporting clinical development.

6.4.4. Breaking the Blind

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment for Periods 1 and 2. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to further clinical development. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information for Periods 1 and 2 will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Dose in Periods 2 and 3 of Cohort 1 may be reduced based on safety and PK observations in previous periods (see Section 4.1). The dose for Cohort 2 (if conducted) will be chosen based on data from Cohort 1 and will not exceed 400 mg Q12 hours.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of sisunatovir greater than 1200 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis if requested by the study medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis

following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. DepoProvera® must be discontinued at least 6 months prior to the first dose of study treatment.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE requiring discontinuation in investigator's view.
- Pregnancy.

If study intervention is permanently discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention. In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. ECG Changes

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 ms.
- Change from baseline: QTcF >60 ms.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.2. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given period are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.3. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Pregnancy;
- Behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study

follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug

shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

Safety/laboratory/analyte results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 340 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1.1. Baseline Procedures

Planned timepoints for medical history and demography are provided in the SoA.

8.2. Efficacy Assessments

Not Applicable.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

3 baseline pre-dose measurements are needed for CQT analysis, these ECGs will be done approximately 30 min, 20 min, and 10 min before the pre-dose meal in Periods 1 and 2, and approximately 30 min, 20 min, and 10 min pre-dose in Period 3. The average of the triplicate ECGs over the 3 pre-dose measurements (total of 9 ECGs) will serve as each participant's baseline QTc value. Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 48 hours after the last dose of study after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection per CRU SOPs. Additional testing may be required by local regulations or by the PI.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention until the follow-up visit (28-35 days after last dose of study drug).
- A male participant who is receiving or has discontinued study intervention inseminates a female partner until the follow-up visit (28-35 days after last dose of study drug) for the participant.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until the follow-up visit (28-35 days after last dose of study drug) for the participant.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

This section is not applicable for this study.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

This section is not applicable for this study.

8.4.8. Adverse Events of Special Interest

This section is not applicable for this study.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

This section is not applicable because there are no medical devices included in the study.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide approximately 0.8 mL plasma, will be collected for measurement of plasma concentrations of sisunatovir as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

CCI [redacted]. Participant confidentiality will be maintained.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.1. Palatability Questionnaire

Participants will be asked to fill out the Palatability Questionnaire after sisunatovir administration for treatments E, F, G, and H. The Palatability Questionnaire will be administered at 1 (immediately after sisunatovir administration), 5, 10, and 20 minutes after sisunatovir administration.

Details of the Palatability Questionnaire are provided in Appendix 10.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

CCI [redacted]

See Appendix 5: Genetics for infonnation regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laborato1y Manual and suppo1ting documentation.

CCI [redacted]

8.7.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

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I [redacted]

CCI [redacted]

See Appendix 5: Genetics for infonnation regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laborato1y Manual and suppo1ting documentation.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summaiy and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primaiy endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

No fonnal statistical hypothesis will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Emolled	"Emolled" means a paiticipant, or their legally authorized representative's, agreement to paiticipate in a clinical study following completion of the info1med consent process and randomization to study intervention. A paiticipant will be considered enrolled if the info1med consent is not withdrawn prior to paiticipating in any study activity after screening. Potential paiticipants who ai·e screened for the pmpose of dete1mining eligibility for the study, but do not paiticipate in the study, are not considered enrolled, unless othe1wise specified by the protocol.
Safety analysis set	All paiticipants randomly assigned to study intervention and who take at least 1 dose of study intervention. Pa1ticipants will be analyzed according to the product they actually received.

Participant Analysis Set	Description
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.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

Details of the analyses will be provided in the Statistical Analysis Plan.

All treatment arms and placebo will be reported separately.

9.3.2. Primary Endpoint(s) Analysis

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, 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 and/or neurological 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.

9.3.2.1. Electrocardiogram Analyses

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		30-60	>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. Changes from baseline will be defined as the change between the post-dose QTcF value and the average of the predose triplicate values on Day 1.

9.3.3. Secondary Endpoint(s) Analysis

Plasma PK parameters of sisunatovir will be derived from the concentration-time data using standard noncompartmental methods of analysis as outlined in Table 4. 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 4. 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 AUC_{tau}	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.

Table 4. Plasma Sisunatovir PK Parameters Definitions

Parameter	Definition	Method of Determination
CL/F	Apparent clearance	Dose/AUC1au
Vz/F*	Apparent volume of distribution	Dose/(AUCtau • ke1)
Rae	Observed accumulation ratio for AUC	AUCtau Day5/AUCtau Dayl
Rac,Cmax	Observed accumulation ratio for Cmax	Cmax Day5/CmaxDayl

* If data permit.

The plasma concentrntions of sisunatovir will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual paiiicipant and summaiy profiles (mean and median plots) of the plasma concentrntion-time data will be plotted by treatment using actual and nominal times, respectively. Mean and median profiles will be presented on both lineai·and semi-log scales.

CCI [redacted]

For the food effect evaluation, natural log transfo1med AUC1au, and Cmax of sisunatovir will be analyzed using a mixed effect model with sequence, and treatment as fixed effects and paiiicipant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and co1Tesponding 90% Cls will be obtained from the model. The adjusted mean differences and 90% Cls 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 400 mg Q12 hours administered under fasted condition) is the Reference treatment and Treatment A (sisunatovir 400 mg Q12 hours administered under fed condition) is the Test treatment. For the food effect compai·ison only the data from treatment A and D will be included in the model.

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" mai·ked by the paiticipant 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. The palatability attributes (mouth feel, bitterness, sweetness, sourness, saltiness, tongue/mouth bmn, overall liking) from the palatability questionnaire (Appendix 10) will be listed and descriptively smnmai·ized and appropriate plots may be generated.

CCI [redacted]

CCI [redacted]

9.4. 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 pmpose of safety assessment, facilitating PK/PD modeling, and/or suppo1iing clinical development.

9.5. Sample Size Determination

A sufficient number of paiiicipants will be screened to achieve 12 paiiicipants randomized to study intervention in Coho1i 1 in the study. Approximately 12 additional paiiicipants may be emolled in Coho1i 2 in the study. The sample size is empirically selected and is not based on statistical power calculation. Paiiicipants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the Investigator.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Financial Disclosure

Not applicable.

10.1.4. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

10.1.5. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.6. Committees Structure

10.1.6.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.7. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan [and monitoring plan] maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly

provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.9. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor's designee (Pfizer CRU)if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related

information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laborato1y tests will be perfo1med at times defined in the Schedule of Activities section of this protocol. Additional laborato1y results may be repo1ted on these samples as a result of the method of analysis or the type of analyzer used by the clinical laborato1y, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laborato1y measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematolo!!V	Chemistrv	Urinalvsis	Other
Hemoglobin Hematocrit RBC count Platelet count WBCcount Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine, CystC eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO2 (bicarbonate) AST,ALT GGT Total bilirnbin Alkaline phosphatase Uric acid Albumin Total protein	Local di12stick: pH• Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laborato1 : Microscopy and culture•	Urine chug screening Pregnancy test (P-hCGl SARS-CoV-2 RT-PCR At screening: • FSHb • Hepatitis B swface antigen • Hepatitis B swface antibody • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency vims

a. Urina1y culture only if deemed appropriate by the investigator.
b. For confinnation of postmenopausal status only.
c. The minimum requirement for chug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Local urine testing will be standard for the protocol unless sernm testing is required by local regulation or IRB/EC. Sernm or urine P-hCG for female participants of childbearing potential.
e. Can be performed on dipstick or pH meter device.
f. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

The investigator must review the laborato1y repo1t, document this review, and record any clinically relevant changes occuning during the study in the AE section of the CRF.

Laborato1y results that could unblind the study and have been collected for the pmpose of the study will not be repo1ted to investigator sites or other blinded personnel until the study has been unblinded.

Any remaining senun/plasma from samples collected for clinical safety laborato1y measurements at baseline and at all times after dose administration ma be retained and stored for the duration of the stud . U on com letion of the stud y, CCI [redacted] These data will not be included in the CSR. Samples to be used for this

purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occmTence in a patient or clinical study pa1ticipant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnonnal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnonnal laborato1y test results (hematology, clinical chemistiy, or minalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measmements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnonnal laborato1y test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/smgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustinents) or discontinuation from the study, significant additional concomitant dmg ti·eatinent, or other therapy.
 	
• Exacerbation of a chronic or intennittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administi·ation, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected dmg-dmg interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be repo1ted as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-hanning intent. Such overdoses should be repo1ted regardless of sequelae.

Events	Meeting the AE Definition
	• Any clinically significant abnonnal laborato1y findings or other abnonnal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the paiticipant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occmTence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the sta1i of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The tenn "life-threatening" in the definition of "serious" refers to an event in which the paiticipant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the paiiicipant has been admitted (usually involving at least an overnight stay) at the hospital or emergency wai·d for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occmTed or was necessaiy, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The te1m disability means a substantial disrnption of a person's ability to conduct n01mal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diaIThea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent eve1yday life functions but do not constitute a substantial disrnption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laborato1y findings indicating an infection in a paiiicipant exposed to a Pfizer product. The te1ms "suspected transmission" and "transinission" ai·e considered synonymous. These cases are considered unexpected and handled as serious expedited cases by phannacovigilance personnel. Such cases ai·e also considered for reporting as product defects, if appropriate.

g. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE repo1iing is appropriate in other situations, such as significant medical events that may jeopai·dize the pa1iicipant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Exainples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of diug dependency or di11g abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for repo1iing SAEs on the CT SAE Repo1i Fonn to Pfizer Safety throughout the active collection period. These requirements ai·e delineated for 3 types of events: (1) SAEs;

(2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Fonn/AE or SAE CRF page.

- There may be instances when copies of medical records for ce1iain cases are requested by Pfizer Safety. In this case, all paiiicipant identifiers, with the exception of the paiiicipant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical infonnation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ied dming the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usualADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or pennanent risk of haim to the reseai·ch participant.

- Severe: A type of AE that inte1n1pts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study inte1vention and each occmTence of each AE or SAE. The investigator will use clinical judgment to dete1mine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be mled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product infonnation, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.

- There may be situations in which an SAE has occuned and the investigator has minimal infonnation to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change their opinion of causality in light of follow-up infonnation and send an SAE follow-up repo1i with the updated causality assessment.

- The causality assessment is one of the criteria used when detennining regulato1y repo1iing requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for repo1iing purposes, as defined by the sponsor. In addition, if the investigator detennines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1i such an assessment in the dedicated section of the CT SAE Report Fonn and in accordance with the SAE repo1iing requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perfo1m or anange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a paiiicipant dies during paiiicipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated infonnation will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The prima1y mechanism for repo1iing an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to repo1i the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper f01m (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a repo1i of a new SAE from a study participant or receives updated data on a previously repo1ied SAE after the electi·onic DCT has been taken off-line, then the site can repo1i this info1mation on a paper SAE f01m (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile ti·ansmission of the CT SAE Report Fonn is the prefe1Ted method to transmit this info1mation to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Fonn sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Repo1i Fonn pages within the designated repo1iing time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom[,and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak,] when having sexual intercourse with a WOCBP who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier

method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must

discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Progestogen only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*.
    - Injectable + barrier*.

Sexual Abstinence

7. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with option 6 for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to sisunatovir or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

- Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	NA	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if >0.7	NA	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤0.9	NA	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	NA	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤0.7	if ≤0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ≤0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 ms.
- New prolongation of QTcF to >480 ms (absolute) or by60 ms from baseline.
- New-onset ati·ial flutter or fibrillation, with conh'olled venti·icular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of>30 seconds' duration.
- Frequent PVCs, triplets, or sho1i intervals (<30 seconds) of consecutive venh'icular complexes.

ECG Findings That May Qualify as SAEs

- QTcF prolongation >500 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex>120 ms).
- New-onset right bundle branch block (QRS complex>120 ms).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free pa1iicipants with ati·ial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Ati·ial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120bpm.
- Sustained supraventi·icular tachycardia (rate >120 bpm) ("sustained" = sho1i duration with relevant symptoms or lasting>1 minute).

- Venti·icular rhythms >30 seconds' dmation, including idiovenu-icular rhythm (HR <40 bpm), accelerated idioventi·icular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heali block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained venti·icular tachyarrhythmias (>30 seconds' dmation).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Au-ial flutter or fibrillation with rapid venti·icular response requiring cardioversion.
- Venti·icular fibrillation/flutter.
- At the discretion of the investigator, any aiThythmia classified as an adverse expenence.

The enumerated list of major events of potential clinical concem are recommended as "alerts" or notifications from the core ECG laborato1y to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be repo1ted as AEs/SAEs.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with sisunatovir for the period of time at least equal to the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

The Sponsor must be consulted for any concomitant medications given to participants enrolled in this study.

Strong and moderate CYP3A4 and P-gp inhibitors or inducers are prohibited, as these medications may have meaningful impact on the pharmacokinetics of sisunatovir.

Sisnunatovir is a CYP3A4 inhibitor and therefore sensitive and narrow therapeutic index CYP3A4 substrates are also prohibited in this study. Since based on in vitro data sisunatovir may be a weak inhibitor of CYP2B6, sensitive narrow TI substrates of CYP2B6 are excluded.

Sisunatovir also may be an inhibitor of OCT1 and MATE1 transporters; therefore, sensitive substrates of these transporters are excluded.

Although his is not all-inclusive, a list of medications that are prohibited in this study is provided below . Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Prohibited Concomitant Medications

CYP3A Inhibitors		CYP3A Inducers	
Moderate	**Strong**	**Moderate**	**Strong**
Aprepitant	Boceprevir	Bosentan	Apalutamide
Ciprofloxacin	Cobicistat	Efavirenz	Carbamazepine
Conivaptan	Danoprevir	Etravirine	Enzalutamide
Crizotinib	Dasabuvir	Phenobarbital	Mitotane
Cyclosporine	Elvitegravir	Primidone	Phenytoin
Diltiazem	Indinavir		Rifampin
Dronedarone	Itraconazole		St. John’s wort
Erythromycin	Ketoconazole		
Fluconazole	Lopinavir		
Fluvoxamine	Paritaprevir		
Imatinib	Ombitasvir		
Tofisopam	Posaconazole		
Verapamil	Ritonavir		

	Saquinavir		
	Telaprevir		
	Tipranavir		
	Telithromycin		
	Troleandomycin		
	Voriconazole		
Sensitive CYP3A Substrates		**CYP3A Substrates with Narrow Therapeutic Index**	
Alfentanil	Lovastatin	Alfentanil	
Atorvastatin	Lurasidone	Astemizole	
Avanafil	Maraviroc	Cisapride	
Budesonide	Midazolam	Cyclosporine	
Buspirone	Naloxegol	Dihydroergotamine	
Darifenacin	Nisoldipine	Ergotamine	
Darunavir	Quetiapine	Fentanyl	
Dasatinib	Sildenafil	Pimozide	
Dronedarone	Simvastatin	Quinidine	
Ebastine	Sirolimus	Sirolimus	
Eletriptan	Tacrolimus	Tacrolimus	
Eplerenone	Ticagrelor	Terfenadine	
Everolimus	Tolvaptan		
Ibrutinib	Tipranavir		
Indinavir	Triazolam		
Felodipine	Vardenafil		
Lomitapide			
Sensitive MATE1 Substrates			
Metformin			
Sensitive CYP2B6 Substrates		**CYP2B6 Substrates with Narrow Therapeutic Index**	
Velpatasvir		Cyclophosphamide	
P-gp Inhibitors		**P-gp Inducers**	
atazanavir	lopinavir	Apalutamide	
boceprevir	lumacaftor	Atazanavir	
cobicistat	mifepristone	Fosamprenavir	
conivaptan	nelfinavir	Lopinavir	
cyclosporine	ombitasvir and paritaprevir and ritonavir and dasabuvir	Rifampicin	
darunavir	posaconazole	st. John's wort (Hypericum perforatum) extract	
diltiazem	ritonavir	Tipranavir	
elvitegravir and cobicistat and emtricitabine and tenofovir DF	saquinavir	Verapamil	
erythromycin	telaprevir		
glecaprevir and pibrentasvir	tipranavir		
indinavir	tucatinib		
itraconazole	verapamil		
ketoconazole	vonoprazan and amoxicillin and clarithromycin		
lonafarnib	voxilaprevir		
Sensitive OCT Substrates			
imatinib			

h. Not an all-inclusive list.

10.10. Appendix 10 : Oral Solution or Suspension Palatability Questionnaire

1. Questionnaire should be administered to adult subjects, preferably by the clinician or the 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	
Subject 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 1 (immediately), 5, 10 and 20 minutes after dosing. Please ensure subject 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.

Q2: Bitterness – Please tell us about the degree of bitterness of the product you tasted.

Q3: Sweetness – Please tell us about the degree of sweet taste of the product you tasted.

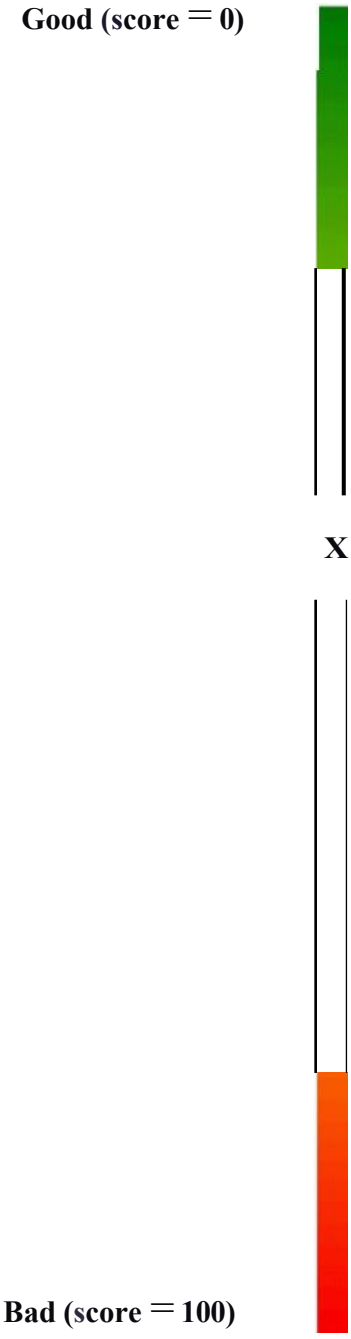
Q4: Sourness – Please tell us about the degree of sour taste of the product you tasted.

Q5: Saltiness – Please tell us about the degree of salty taste of the product you tasted.

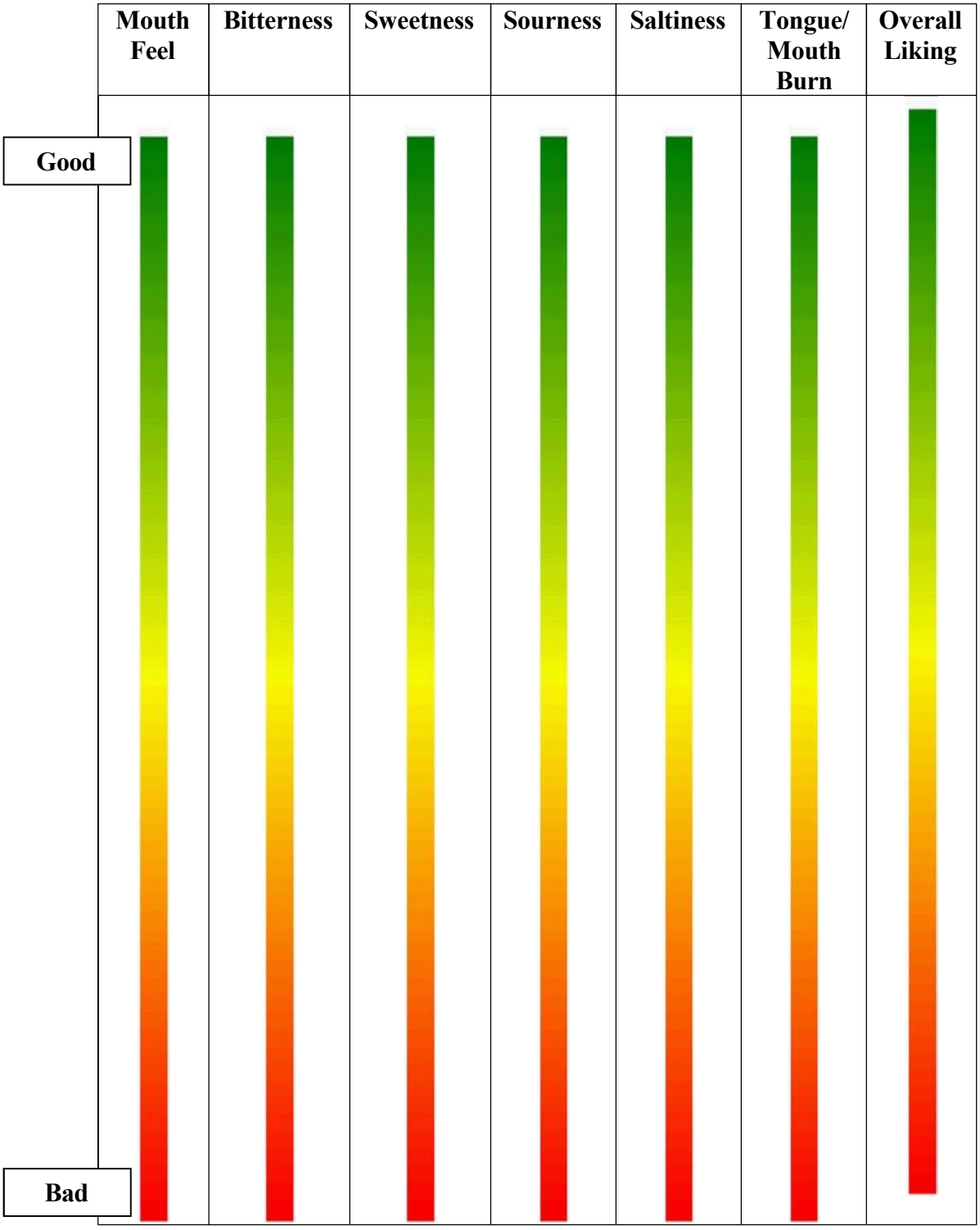
Q6: Tongue/mouth burn – Please tell us about the degree of tongue/mouth burn of the product you tasted.

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

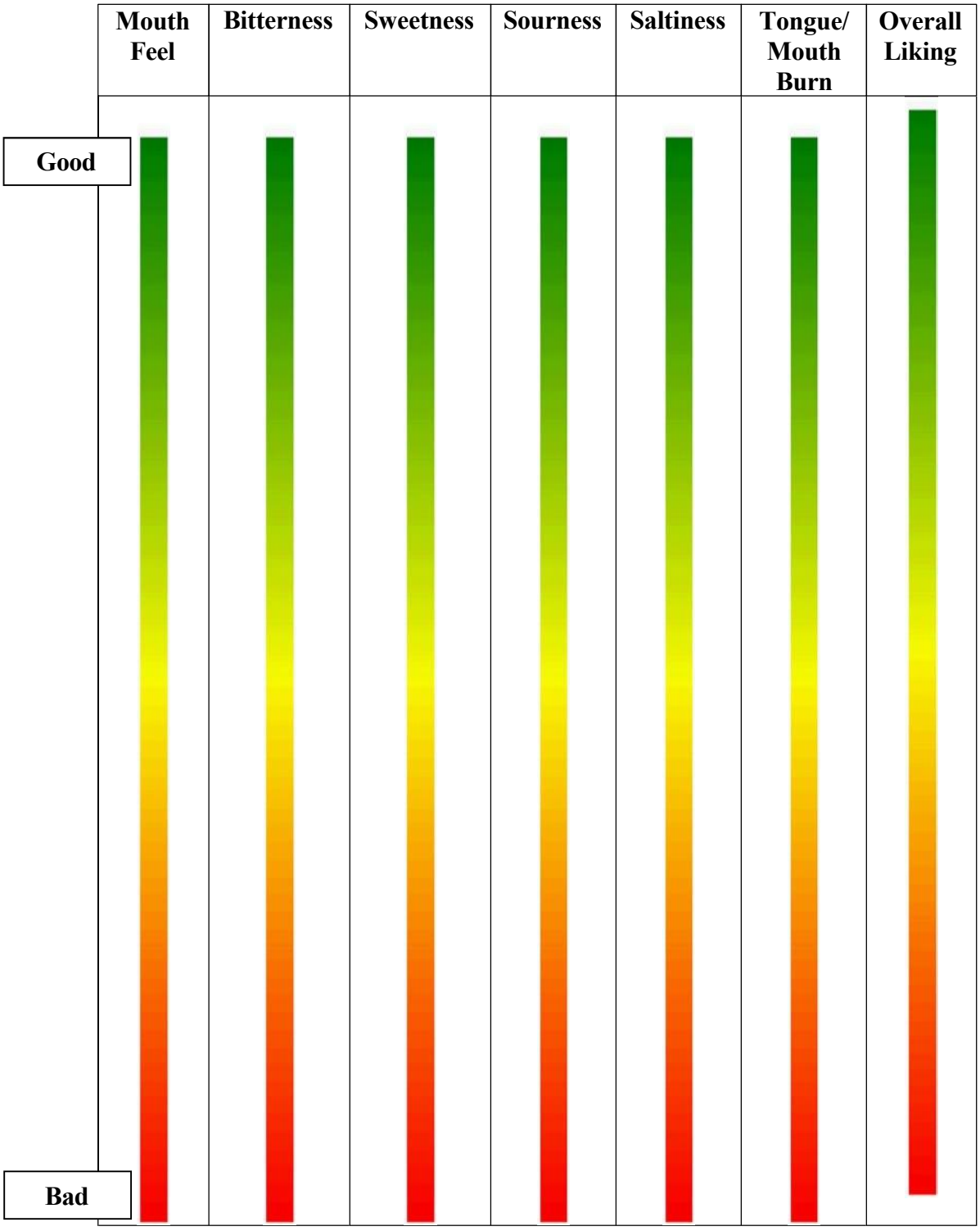
Example: How to provide a mark (X) on the color bar.



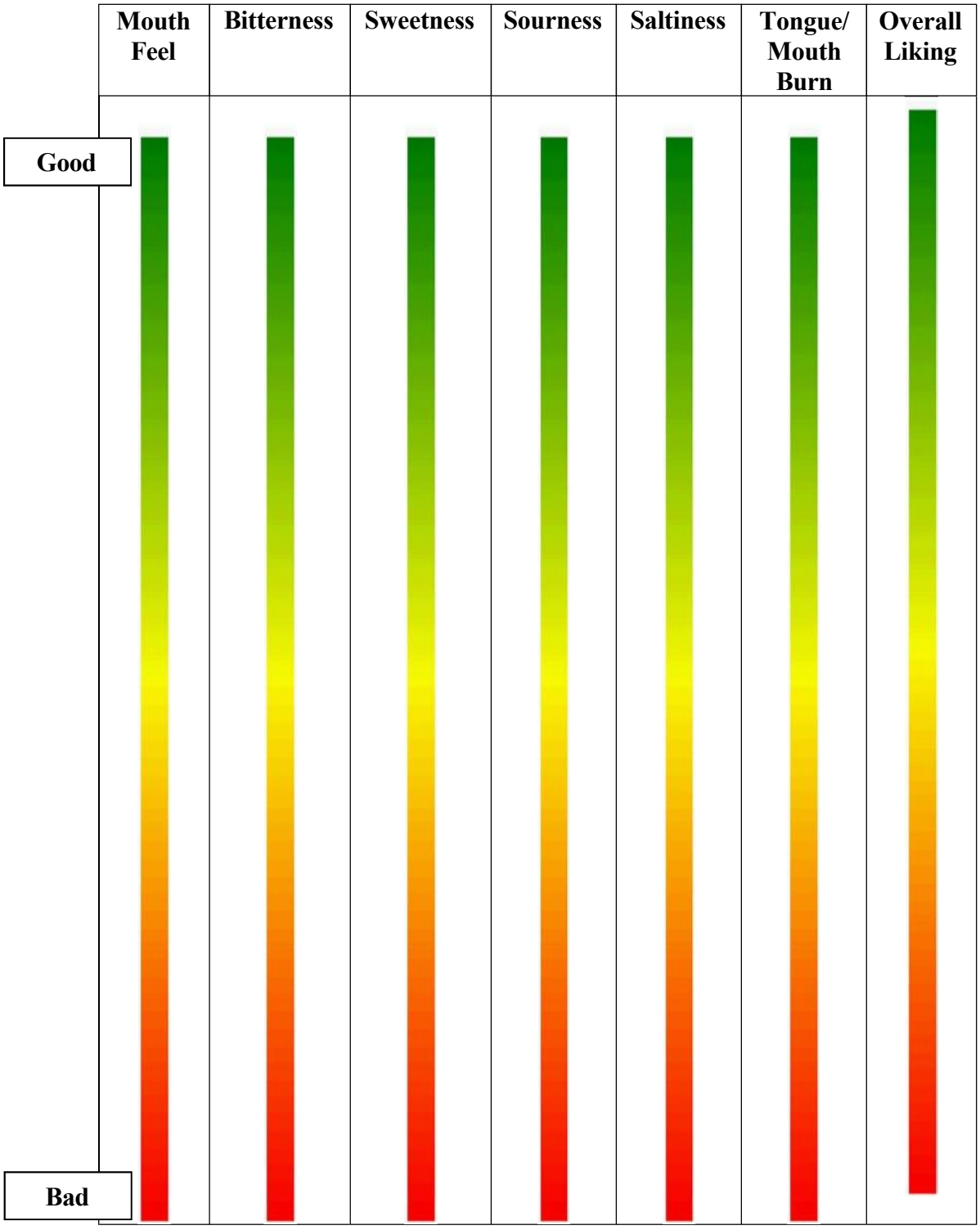
Within 1 minute (immediately) after dosing
Collection time: _____
Provide a mark (X) <u>on the color bar</u>.



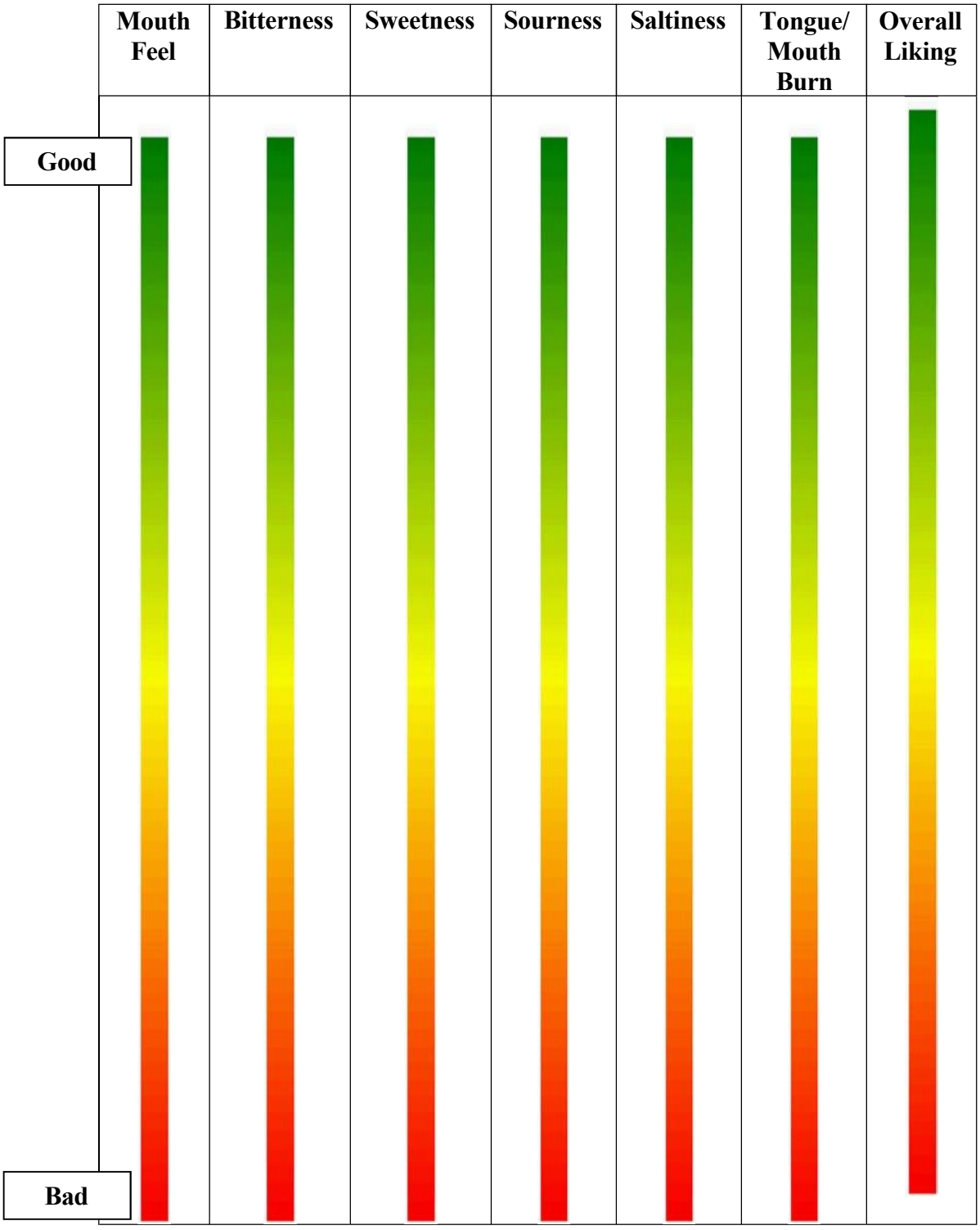
5 minutes after dosing
Collection time: _____
Provide a mark (X) on the color bar.



10 minutes after dosing
Collection time: _____
Provide a mark (X) on the color bar.



20 minutes after dosing
Collection time: _____
Provide a mark (X) <u>on the color bar.</u>



Additional Feedback – After completing the "20 minute after dosing" palatability questions, please provide any additional descriptive feedback in the box below regarding the taste or odor of the drug.

10.11. Appendix 11: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
%CV	percent coefficient of variation
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
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}
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
β-hCG	β-human chorionic gonadotropin
BID	twice-daily dosing
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
C_{max}(dn)	dose normalized maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CCI	[redacted]
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial

Abbreviation	Term
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CV	cardiovascular
CYP	cytochrome P450
D1-4	day 1 to 4
D5	day 5
DCT	data collection tool
DDI	drug-drug interaction
DIC	drug in capsule
DILI	drug-induced liver injury
DPB	sisunatovir dry powder blend
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBP cyclodextrin	hydroxypropyl-β-cyclodextrin
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy

Abbreviation	Term
HRU	healthcare resource utilization
Ht	height
IB	Investigator's Brochure
CCI	[redacted]
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IV	intravenous(ly)
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LRTI	lower respiratory tract infection
MAD	multiple ascending dose
MATE	multidrug and toxin extrusion
MQI	medically qualified individual
MTD	Maximum tolerated dose
NA	not applicable
NIMP	noninvestigational medicinal product
CCI	[redacted]
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporting
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PE	physical examination
P-gp	p-glycoprotein
PI	principal investigator
PIMS	Phase One Management System
PK	pharmacokinetic(s)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time

Abbreviation	Term
PVC	premature ventricular contraction/complex
Q12	every 12
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
R_{ac}	observed accumulation ratio for AUC
$R_{ac,Cmax}$	observed accumulation ratio for C_{max}
RBC	red blood cell
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
SAD	single ascending dose
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
Scr	serum creatinine
Scys	serum cystatin C
SD	single dose
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal elimination half-life
T^3	total triiodothyronine
T^4	total thyroxine
TB	tuberculosis
T bili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
TOC	table of contents
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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