Title Page

A PHASE 1, RANDOMIZED, OPEN-LABEL, 2-PART CROSSOVER STUDY TO ASSESS THE RELATIVE BIOAVAILABILITY OF SISUNATOVIR FOLLOWING SINGLE ORAL DOSE OF DIFFERENT FORMULATIONS UNDER FED AND FASTED CONDITIONS IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07923568
Study Intervention Name:	Sisunatovir
US IND Number:	143479
EU CT Number:	2023-505228-79-00
ClinicalTrials.gov ID:	NCT05994963
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5241013
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A Study to Learn How Different Manufactured Products of the Study Medicine Called Sisunatovir are Taken Up Into the Blood When Taken on an Empty Stomach or When Taken With a Meal in Healthy Adults

Document History

Document	Version Date
Amendment 1	09 November 2023
Original protocol	07 June 2023

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 Summary of Changes Table

Amendment 1 (09 November 2023)

Overall Rationale for the Amendment: The overall rationale for this amendment is to add Part 2 for the evaluation of a low-fat meal on sisunatovir exposure with the WGT formulation.

Description of Change	Brief Rationale	Section # and Name
	Substantial Modification(s)	
Updated protocol title to "2-PART CROSSOVER STUDY"	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Title page and Section 1.1 Synopsis
Divided secondary objective/endpoint into high-fat meal and low-fat meal	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.1 Synopsis and Section 3 Objectives and Endpoints
Clarified the "fed condition" in the original study design (ie, Part 1) as "with a high-fat meal"	Clarified per the new study design	Section 1.1 Synopsis, Section 3 Objectives and Endpoints, Section 4.1 Overall Design, Section 4.2 Scientific Rationale for Study Design, Section 5.3.2 Meals and Dietary Restrictions, Section 6.1 Study Intervention(s) Administered, and Section 9.3.3 Secondary Endpoint(s) Analysis
Updated overall study design by re-defining the original study design as	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.1 Synopsis and Section 4.1 Overall Design

Description of Change	Brief Rationale	Section # and Name
Part 1 and adding a new Part 2, and added Treatment D – sisunatovir CCI mg WGT administered with a low-fat meal in Part 2		
Updated the total number of participants to be enrolled in this study to "between 12 and 24", including approximately 12 participants in Part 1 and approximately 12 participants in Part 2	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.1 Synopsis
Added schedule of assessments and PK sampling schedule for Part 2	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.3 Schedule of Activities
Added the study arms and duration information for Part 2	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.1 Synopsis and Section 4.1 Overall Design
Updated the statistical methods for the high-fat food effect evaluation in Part 1 and low-fat food effect evaluation in Part 2	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.1 Synopsis and Section 9.3.3.2 Other Secondary Endpoints Analyses
Corrected the follow-up period interpreted as Study Day to "D35-43" for Part 1	Correction in alignment with the follow-up period defined in this protocol (ie, follow-up will occur 28 to 35 days after last dose)	Section 1.3 Schedule of Activities Table 1
Updated the rationale for this study to reflect the evaluations for high- and low-fat food effects	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 1.1 Synopsis and Section 2.1 Study Rationale
Updated the scientific rationale for study design based on the preliminary PK data from Part 1	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 4.2 Scientific Rationale for Study Design
Updated the definitions for end of study and a participant completing the study	To align with the updated study design	Section 4.4 End of Study Definition

Description of Change	Brief Rationale	Section # and Name
Updated meals and dietary restrictions to reflect the restrictions for high- and low-fat meals	To align with the updated study design	Section 5.3.2 Meals and Dietary Restrictions
Added administration details for Part 2	Evaluation of effect of a low-fat meal on exposure of WGT formulation	Section 6.1.1.2 Part 2
Updated total blood sampling volume	Additional Part 2	Section 8.1 Administrative and Baseline Procedures
Clarified that participants who have completed Part 1 are eligible to participate in Part 2.	Additional Part 2	Section 1.1 Synopsis, Section 4.1 Overall Design, and Section 4.2 Scientific Rationale for Study Design.
Non-substantial Modification(s)		
Updated ClinicalTrials.gov ID	Update per available information	Title page and Section 1.1 Synopsis

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Randomized, Open-Label, 2-Part Crossover Study to Assess the Relative Bioavailability of Sisunatovir Following Single Oral Dose of Different Formulations Under Fed and Fasted Conditions in Healthy Adult Participants

Brief Title:

A Study to Learn How Different Manufactured Products of the Study Medicine Called Sisunatovir are Taken Up Into the Blood When Taken on an Empty Stomach or When Taken With a Meal in Healthy Adults

Regulatory Agency Identification Number(s):

US IND Number:	143479
EU CT Number:	2023-505228-79-00
ClinicalTrials.gov ID:	NCT05994963
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C5241013
Phase:	1

Rationale:

This study is designed to assess safety, tolerability, pharmacokinetics (PK), and food effect of a single oral dose of 2 different formulations of sisunatovir. The oral PK of a new Wet Granulation Tablet (WGT) formulation potentially to be used in future clinical studies will be compared with that of current Powder in Capsule (PIC) used in completed and other ongoing clinical studies. Additionally, the high- and low-fat food effects on the oral PK of the new WGT formulation will be evaluated.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To determine the relative bioavailability of sisunatovir following a single oral dose of CCI mg as PIC vs WGT in a fasted state	• AUC_{last}, AUC_{inf} (if data permit*), and C_{max} of PIC vs WGT
Secondary:	**Secondary:**
• To determine the effect of a high-fat meal on the relative bioavailability of sisunatovir following a single oral dose of CCI mg as WGT	• AUC_{last}, AUC_{inf} (if data permit*), and C_{max} of WGT under fasted vs with a high-fat meal

Objectives	Endpoints
• To determine the effect of a low-fat meal on the relative bioavailability of sisunatovir following a single oral dose of CCI mg as WGT	• AUC_{last}, AUC_{inf} (if data permit*), and C_{max} of WGT under fasted vs with a low-fat meal
• To characterize the safety and tolerability following a single oral dose of CCI mg of sisunatovir as PIC or WGT in a fasted state, or as WGT in a fed state	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs

*Should it be deemed that too few AUC_{inf} estimates (eg, less than 10 for a single dose) are obtained from the evaluable participants, AUC_{last} may be selected as the primary/secondary endpoint for CSR reporting.
Abbreviations: AUC_{inf} = area under the concentration-time curve from time 0 to infinity; AUC_{last} = area under the concentration-time curve from 0 to time of last measurable concentration; C_{max} = maximum observed concentration; CSR = clinical study report; ECG = electrocardiogram; TEAE = treatment-emergent adverse event.

Overall Design:

This is a Phase 1, randomized, open-label, 2-part crossover study to evaluate the PK, food effect, safety, and tolerability of sisunatovir CCI mg single dose administered as PIC or WGT under fasted conditions, or as WGT with food.

Part 1

Participants will be admitted to the clinical research unit (CRU) on Day -1 to undergo baseline procedures. Over the first 2 periods, all participants are planned to receive 1 dose of (A) sisunatovir CCI mg as PIC and 1 dose of (B) sisunatovir CCI mg as WGT in a fasted state. All participants in Period 3 will receive 1 dose of (C) sisunatovir CCI mg as WGT with a high-fat meal. There is an at least 72-hour washout period between the dose of 2 adjacent periods.

Part 1 Study Design

	Period 1	Period 2	Period 3
Sequence 1 (N=6)	A	B	C
Sequence 2 (N=6)	B	A	C

All study interventions will be administered as a single dose of CCI-mg sisunatovir as PIC or WGT.
A= PIC under fasted condition; B = WGT under fasted condition; C= WGT with a high-fat meal.

Part 1 consists of an initial screening period of up to 28 days (while allowing for the return and review of all results, including laboratory tests), a 10-day inpatient stay at the CRU which includes 3 periods, and a follow-up contact that will occur 28-35 days after the last administration of sisunatovir. For individual participants, the total duration of participation from the screening visit to the follow-up visit or phone call will range from approximately 6 weeks (minimum) to approximately 10 weeks (maximum).

Approximately 12 participants will be randomized into 2 sequences with approximately 6 participants in each. For each sequence, participants will receive study interventions in a pre-specified manner as listed in the table for Part 1 Study Design. Participants who

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

Part 2

Participants will be admitted to the CRU on Day -1 to undergo baseline procedures. All participants are planned to receive 1 dose of (B) sisunatovir [CCI] mg as WGT in a fasted state and 1 dose of (D) sisunatovir [CCI] mg as WGT with a low-fat meal. There is an at least 72-hour washout period between Period 1 and Period 2. Participants who have participated in Part 1 are eligible to participate in Part 2.

Part 2 Study Design

	Period 1	Period 2
Sequence 1 (N=6)	B	D
Sequence 2 (N=6)	D	B

All study interventions will be administered as a single dose of [CCI]-mg sisunatovir as WGT.
B = WGT under fasted condition; D= WGT with a low-fat meal.

Part 2 consists of an initial screening period of up to 28 days, a 7-day inpatient stay at the CRU which includes 2 periods, and a follow-up contact that will occur 28-35 days after the last administration of sisunatovir. For individual participants, the total duration of participation from the screening visit to the follow-up visit or phone call will range from approximately 6 weeks (minimum) to approximately 10 weeks (maximum).

Approximately 12 participants will be randomized into 2 sequences with approximately 6 participants in each. For each sequence, participants will receive study interventions in a pre-specified manner as listed in the table for Part 2 Study Design. 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 Part 1 and approximately 12 participants will be enrolled in Part 2. Some participants may participate in both Parts 1 and 2, therefore the total number of participants in this study will be between approximately 12 and 24.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to study intervention.

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:

Age and Sex: Male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac evaluation.

Exclusion Criteria

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

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).

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions 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 cytochrome P450 3A (CYP3A) inducers or time-dependent inhibitors which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

Prior/Concurrent Clinical Study Experience:

4. 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:

5. A positive urine drug test, confirmed by a repeated test, if deemed necessary.

6. For participants <60 years: screening supine blood pressure (BP) ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. For participants ≥60 years old, a screening supine BP of ≥150/90 mm Hg may be used. If systolic BP is ≥ 140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

7. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTc corrected using Fridericia's formula [QTcF] >450 ms, complete left bundle branch block [LBBB], signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree atrioventricular [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.

8. 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: estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 based on chronic kidney disease epidemiology (CKD-EPI) equation; aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level ≥1.05× upper limit of normal (ULN); gamma-glutamyl transferase (GGT) >1.05× ULN; alkaline phosphatase (ALP) >1.05× ULN; total bilirubin level ≥1.05× 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:

For individual participants, the total duration of participation from the screening visit to the follow-up visit will range from approximately 6 weeks (minimum) to approximately 10 weeks (maximum) for each of Part 1 and Part 2.

Study Intervention(s)	
Intervention Name	Sisunatovir
Use	Experimental
Investigational Medicinal Product (IMP) or Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AxMP)	IMP
Dose Formulation	PIC or WGT
Unit Dose Strength(s)	CCI mg for PIC or CCI mg for WGT
Route of Administration	Oral

Part 1 Study Arm(s)			
Arm Title	Treatment A	Treatment B	Treatment C
Arm Description	Participants will receive a single [CCI] mg dose of sisunatovir PIC administered orally as [CCI] sisunatovir [CCI]-mg capsules under a fasted condition.	Participants will receive a single [CCI] mg dose of sisunatovir WGT administered orally as [CCI] sisunatovir [CCI]-mg tablets under a fasted condition.	Participants will receive a single [CCI] mg dose of sisunatovir WGT administered orally as [CCI] sisunatovir [CCI]-mg tablets with a high-fat meal.

Part 2 Study Arm(s)		
Arm Title	Treatment B	Treatment D
Arm Description	Participants will receive a single [CCI] mg dose of sisunatovir WGT administered orally as [CCI] sisunatovir [CCI]-mg tablets under a fasted condition.	Participants will receive a single [CCI] mg dose of sisunatovir WGT administered orally as [CCI] sisunatovir [CCI]-mg tablets with a low-fat meal.

Statistical Methods:

A sufficient number of participants will be screened to achieve approximately 12 participants randomized to study intervention in each of Part 1 and Part 2. The sample size is empirically selected and is not based on statistical power calculation.

Part 1

To compare the Treatments A (PIC under fasted condition) and B (WGT under fasted condition), natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of sisunatovir will be analyzed separately using a mixed effect model with sequence (AB or BA), period and treatment included as fixed effects and participant nested within sequence as a random effect. Only data from the first 2 study periods will be used in the analysis. Treatment A is the Reference treatment and Treatment B is the Test treatment.

For the high-fat food effect evaluation, natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of sisunatovir will be analyzed using a mixed effect model with sequence, and treatment as fixed effects and participant within sequence as a random effect. Only data from Treatment B (WGT under fasted conditions) and Treatment C (WGT with a high-fat meal) will be included in the model. Treatment B is the Reference treatment, Treatment C is the Test treatment.

Part 2

For the low-fat food effect evaluation, natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of sisunatovir will be analyzed using a mixed effect model with sequence, and treatment as fixed effects and participant within sequence as a random effect. Data from Treatment B (WGT under fasted conditions) and Treatment D (WGT with low-fat meals) will be included in the model. Treatment B is the Reference treatment, Treatment D is the Test treatment.

Part 1 and Part 2

Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Ethical Considerations:

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

1.2. Schema

Not applicable.

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 information 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 participant.

Table 1. Study Schedule of Assessment (Part 1)

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Screen	Admission	Periods 1-3			Period 3	F/U	ET	Notes
Days Relative to Day 1 for Each Period			D1	D2	D3	D4			• Screening ≤28 days before the first dose. • Follow-up may occur via telephone contact and will occur 28 to 35 days after last dose.
Part 1 Study Day	D-28 to D-2	D-1	D1/4/7	D2/5/8	D3/6/9	D10	D35-43		
Informed consent	X								• Informed consent must be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	X			• Participants will be admitted to the CRU on Day -1.
Inclusion/exclusion criteria	X	X							
Medical/medication history	X	X							• Procedure to be completed prior to dosing in Period 1.
Physical exam	X	X						X	• PE at Screening or Admission only. A brief PE at other times may be performed at the discretion of the investigator. • Including height and weight at screening only.
Safety laboratory	X	X	X			X		X	• Participants should fast for at least 4 hours before safety labs are drawn. • Safety lab on Day -1 will serve as pre-dose safety lab for Period 1, so no safety lab on Period 1 Day 1. Safey lab will be collected prior to dosing on Day 1 of Periods 2 and 3. • Includes hematology, chemistry, and urinalysis, which are listed in Appendix 2.
Demography	X								
Pregnancy test (WOCBP only)	X	X						X	• ET pregnancy testing only if participant withdraws while not admitted to the CRU. • See Section 8.3.5.
Contraception check	X	X				X	X	X	

Table 1. Study Schedule of Assessment (Part 1)

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Screen	Admission	Periods 1-3			Period 3	F/U	ET	Notes
Days Relative to Day 1 for Each Period			D1	D2	D3	D4			• Screening ≤28 days before the first dose. • Follow-up may occur via telephone contact and will occur 28 to 35 days after last dose.
Part 1 Study Day	D-28 to D-2	D-1	D1/4/7	D2/5/8	D3/6/9	D10	D35-43		
FSH (post-menopausal women only)	X								
Urine drug testing	X	X							
Single 12-Lead ECG	X		X			X		X	
BP and pulse rate	X		X			X		X	• Day 1 of each Period prior to dose and on discharge day.
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X								
Study intervention administration			X						• Period 1 and Period 2 are dosed in a fasted state. • Period 3 is dosed in a fed state.
PK blood sampling			X	X	X	X		X	• Detailed PK schedule in Table 3.
CRU discharge						X			• Participants will be discharged from the unit on Day 4 of Period 3 (Study Day 10).
Serious and nonserious AE monitoring	X	→	→	→	→	→	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 2. Study Schedule of Assessment (Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Screen	Admission	Periods 1-2			Period 2	F/U	ET	Notes
Days Relative to Day 1 for Each Period			D1	D2	D3	D4			• Screening ≤28 days before the first dose. • Follow-up may occur via telephone contact and will occur 28 to 35 days after last dose.
Part 2 Study Day	D-28 to D-2	D-1	D1/4	D2/5	D3/6	D7	D32-39		
Informed consent	X								• Informed consent must be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	X			• Participants will be admitted to the CRU on Day -1.
Inclusion/exclusion criteria	X	X							
Medical/medication history	X	X							• Procedure to be completed prior to dosing in Period 1.
Physical exam	X	X						X	• PE at Screening or Admission only. A brief PE at other times may be performed at the discretion of the investigator. • Including height and weight at screening only.
Safety laboratory	X	X	X			X		X	• Participants should fast for at least 4 hours before safety labs are drawn. • Safety lab on Day -1 will serve as pre-dose safety lab for Period 1, so no safety lab on Period 1 Day 1. Safey lab will be collected prior to dosing on Day 1 of Periods 2. • Includes hematology, chemistry, and urinalysis, which are listed in Appendix 2.
Demography	X								
Pregnancy test (WOCBP only)	X	X						X	• ET pregnancy testing only if participant withdraws while not admitted to the CRU. • See Section 8.3.5.
Contraception check	X	X				X	X	X	
FSH (post-menopausal women only)	X								
Urine drug testing	X	X							
Single 12-Lead ECG	X		X			X		X	
BP and pulse rate	X		X			X		X	• Day 1 of each Period prior to dose and on discharge day.

Table 2. Study Schedule of Assessment (Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	Screen	Admission	Periods 1-2			Period 2	F/U	ET	Notes
Days Relative to Day 1 for Each Period			D1	D2	D3	D4			• Screening ≤28 days before the first dose. • Follow-up may occur via telephone contact and will occur 28 to 35 days after last dose.
Part 2 Study Day	D-28 to D-2	D-1	D1/4	D2/5	D3/6	D7	D32-39		
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X								
Study intervention administration			X						
PK blood sampling			X	X	X	X		X	• Detailed PK schedule in Table 4.
CRU discharge						X			• Participants will be discharged from the unit on Day 4 of Period 2 (Study Day 7).
Serious and nonserious AE monitoring	X	→	→	→	→	→	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 3. Detailed PK Sampling Schedule (Part 1)

Visit Identifier	Periods 1-3													Period 3	Notes
Period Day	1										2		3	4	
Hours After Morning Dose	0	1	2	3	4	5	6	8	10	12	24	36	48	72	Hour 0 = predose sample collection
Study intervention administration	X														
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Predose sample collected in Periods 2 and 3 are 72 hours postdose PK sample for Periods 1 and 2, respectively.

Table 4. Detailed PK Sampling Schedule (Part 2)

Visit Identifier	Periods 1 and 2													Period 2	Notes
Period Day	1										2		3	4	
Hours After Morning Dose	0	1	2	3	4	5	6	8	10	12	24	36	48	72	Hour 0 = predose sample collection
Study intervention administration	X														
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Predose sample collected in Period 2 are 72 hours postdose PK sample for Period 1.

2. INTRODUCTION

Sisunatovir (PF-07923568, formerly RV521) is an orally administered [redacted] for the treatment of adult and pediatric patients with RSV.

2.1. Study Rationale

The purpose of the study is to assess the PK, safety, and tolerability of a single oral dose of 2 different formulations of sisunatovir when administered under fasting conditions. The oral PK of a new WGT formulation potentially to be used in future clinical studies will be compared with that of PIC formulation used in completed and ongoing clinical studies. Additionally, the high- and low-fat food effects on the oral PK of the new WGT formulation will be evaluated.

2.2. Background

RSV is ubiquitous and known to infect almost all children by 2 years of age.[1] The clinical manifestation of RSV infection is typically mild URTI. However, in infants, young children, immunocompromised and the elderly, it can cause severe LRTI leading to hospitalization, ICU admission and even death.[2] [3,4]

The current management of RSV infection includes limited treatment measures, primarily consisting of supportive care. There are, as yet, only 2 approved antivirals. The first, ribavirin, is a nucleoside analogue, but clinical use is restricted due to its limited antiviral potency, delivery route, toxicity and teratogenic potential.[5] The other is the monoclonal antibody Synagis (palivizumab) which interacts with F glycoprotein of the RSV virus and has been approved in the US and EU.[6,7] Palivizumab has been shown to provide protection in infants at risk of severe disease, but needs to be given before infection and is administered monthly throughout the winter season.[7] It is approved for use in infants with a history of prematurity, hemodynamically significant cardiac disease or chronic lung disease of prematurity. Recently (November 2022), Nirsevimab, a monoclonal antibody to the RSV F protein that has an extended half-life, was approved for prevention of RSV-LRTI in newborns and infants during their first RSV season in the EU.[8] There remains, however, an ongoing unmet clinical need for an effective therapy for RSV disease in children, and a number of new treatments are in development.

Sisunatovir (PF-07923568) is a potent inhibitor of [redacted] In this way, F protein inhibition may reduce both viral replication and pathology, reducing the severity of RSV-LRTI. Thus, sisunatovir may provide clinical benefit to pediatric participants with RSV disease.

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 CCI [redacted] Sisunatovir treatment resulted in a significant reduction in CCI [redacted]

CCI [redacted]

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

More details are presented in the IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In animal PK studies sisunatovir showed slow oral absorption, moderate-high CL, high volume of distribution, and oral bioavailability of 46%, 42%-132%, and 63% in mouse, rat, and dog, respectively.

Plasma protein binding of sisunatovir was low to moderate across species, with average fraction unbound of 0.381, 0.524, 0.266, 0.480 and 0.667 in mouse, rat, dog and guinea pig, and human 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 44 mg/kg to 150 mg/kg.

In vitro studies indicate that CYP3A4 is the main CYP isoform that metabolizes sisunatovir with minor contribution from CYP2D6. Results of a clinical DDI study (C5421004), using CCI [redacted]

Based on in vitro studies, the PK of OCT1 and MATE1 substrates may be altered when co-administered with sisunatovir, and therefore sensitive OCT1 and MATE1 substrates are prohibited in this study (Section 10.8).

In vitro studies also indicate there is a risk of inhibition of CYPs 1A2, 2B6, 2C9, 2C19, and 3A4. The DDI with CYPs 1A2, 2B6, 2C9, and 2C19 is predicted to be minimal (predicted less than 25% increase in AUC of a sensitive substrate).

In vitro studies indicate that sisunatovir is likely a P-gp substrate; therefore, co-administration of inhibitors for the transporter (P-gp) may result in increased exposure to sisunatovir. A clinical DDI study (C5241004) indicated that CCI [redacted] (Section 10.8).

More details are presented in the IB.

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, heart (degeneration/necrosis of the myocardium) and lung (vascular degeneration/necrosis) at 240 mg/kg/day (non-tolerated dose) and trachea (epithelial degeneration and/or 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.

More details are presented in the IB.

2.2.4. Clinical Overview

To date, 5 clinical studies of sisunatovir have been completed; of these, 4 studies were conducted in healthy adults. Key design features of the completed clinical studies in healthy adults are provided in Table 5, and summaries of the key clinical pharmacology, clinical efficacy and clinical safety data from the completed studies are provided in the sections below.

Table 5. Completed Sisunatovir Clinical Studies

Study Number (Status)	Study Type / Key Design Features	Study Population/N	Dose, Dosing Regimen	Formulation Used
C5241001 (previously REVC001)	Phase 1, randomized, double-blind, placebo-controlled, safety, tolerability, PK, food-effect of SAD and MAD	Healthy participants Part A (SAD): 24 Caucasian and 12 Japanese	Part A: CCI [redacted] mg	DIC[a]
		Part B (MAD): 24	Part B: CCI [redacted] mg BID × CCI days for a total of CCI doses	DIC[a]
		Part C (food effect and formulation): 16	Part C: CCI mg	DIC[a] Liquid Formulation[a]
C5241002 (previously REVC002)	Phase 2a, randomized, double-blind, placebo-controlled	Healthy participants inoculated with RSV challenge virus: 66	CCI mg or CCI mg BID × CCI days for a total CCI doses	DIC
C5241004 (previously REVC004)	Phase 1, adaptive, part randomized, part open-label, drug interactions, safety, tolerability	Healthy participants Midazolam – 22 Itraconazole – 20 Verapamil – 20 Rifampicin – 20	As perpetrator: CCI mg BID × CCI days As victim: CCI mg single dose before and after inducer/inhibitor treatment	DIC
C5241005 (previously REVC005)	Phase 1, open-label, single-dose, PK, safety, and tolerability study	Healthy participants: 9	CCI mg, CCI single doses in total 1 × DIC (fed) 1 × PIC (DPB) dispersed in H_2O (fed) 1 × PIC (DPB) dispersed in H_2O (fasted) [wash-out: 3 days between each of the 3 dosing days]	DIC PIC (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 hydroxypropyl-β-cyclodextrin (HBP cyclodextrin), Lycasin, flavoring agent (strawberry), benzoic acid and water, and 68 participants received DIC in the study.

Completed Pediatric Study:

- C5241003 was an ex-US Phase 2 study to characterize the PK profile and safety to sisunatovir in RSV-infected hospitalized children aged 1-36 months (recruitment completed December 2022; clinical study report in preparation). 51 pediatric patients hospitalized due to RSV-LRTI received either a single dose (N=19) or up to 5 days multiple dose (q12h) (N=32) of sisunatovir or placebo. Participants 1 to <6 months of age were administered sisunatovir up to 2.5 mg/kg q12h (q12h) for 5 days.

Participants 6 to 36 months of age were administered sisunatovir up to 5.0 mg/kg q12h for 5 days.

Ongoing Studies:

- C5241006 is an ongoing Phase 1 study in healthy participants to evaluate the pharmacokinetics, safety and tolerability of multiple oral doses of placebo, CCI mg, or CCI mg CCI sisunatovir when administered with food or in a fasting state and the palatability of a single dose of sisunatovir.

- C5241008 is an ongoing Phase 1 study to assess the absorption, metabolism, and elimination (AME) and recovery of [14C]-sisunatovir. The resulting data will provide more detailed information to better understand the AME characteristics of sisunatovir in humans and to guide further development of the compound.

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 05 December 2022, 51 pediatric patients hospitalized due to RSV-LRTI have received either a single dose (N=19) or multiple BID doses of sisunatovir up to 5 days in the ongoing C5241003 study (N=32).

In adult studies, 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. The most commonly reported treatment related TEAEs in adults were in the GI disorders System Organ Class: nausea, diarrhea and abdominal pain. These TEAEs have been mild to moderate in intensity and resolved without sequelae.

As of 28 October 2022, there have been no SAEs attributable to sisunatovir and no deaths in the clinical studies. There has been one serious AE of fever reported in the pediatric study (C5241003) in a child hospitalized with RSV infection who received a single dose of sisunatovir. This was considered serious because it prolonged hospitalization, but the SAE was reported as not related to IMP. In Study C5241002, there was 1 SAE of sub-acute myocarditis reported for a participant on placebo; this was considered to be causally related to the challenge virus.

In adults, sisunatovir is slowly absorbed reaching maximum plasma concentrations (T_{max}) at 4-6 hours with a half-life of 7-10 hours in healthy participants. Steady-state concentrations were reached after approximately 2 days of dosing and a 2-4 fold accumulation of exposure following a Q12h dose regimen. AUC and C_{max} values increased in a greater than dose proportional manner across single and multiple dose studies. Following 5 days of dosing in C5241001 and C5241002, the variability in PK parameters was high, with %CV ranging from 67.4%-127% for C_{max} and 61.7%-116% for AUC_{12}.

The effect of food on the single dose PK was assessed for the DIC and PIC (DPB) dispersed in water (Studies C5241001 and C5241005). 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 190% (90% CI: 86.2% - 418%) for AUC_{inf}. It should be noted that the DIC fasted results from C5241001 were lower than typically seen in other studies with CCI mg administered under fasting conditions, resulting in an artificially higher ratio of fed/fasted in this study. For the PIC (DPB) dispersed in water the extent of systemic exposure to sisunatovir (geometric mean AUC_{inf}) under fed and fasted conditions was 403 and 516 ng•h/mL, respectively, with the between-subject variability being slightly lower under fasted conditions (%CV 69.1% compared with 79.6%). The ratio of fed/fasted was 74.2% (90% CI: 39.0% – 141%) for C_{max} and 77.7% (90% CI: 44.8% – 135%) for AUC_{inf}.

Study C5241004 demonstrated that the disposition of sisunatovir is 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 CCI mg and CCI mg sisunatovir dose groups respectively (dosed CCI for CCI 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, CCI mg sisunatovir and CCI 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 (84.26%) and p=0.002 (83.76%), (Wilcoxon Rank Sum test) for the CCI mg and CCI mg sisunatovir dose groups, respectively.

No participant in Study C5241001 had a QTcF interval change from baseline >30 msec. Furthermore, no significant QTc prolongation was detected in C-QT analyses performed in SAD participants (C5241001), MAD participants (C5241001) or DDI study participants (C5241004).

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 PK, food effect, safety, and tolerability 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 2.2.3. The clinical impact of these potential risks will be minimized through standard, intensive, inpatient monitoring of the participants following administration 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. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

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. To date, mild transient elevations of liver enzymes have been observed in a few participants within clinical studies.	Safety monitoring including laboratory (ie, transaminases, 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 completed adult clinical studies sisunatovir has been associated with mild GI AEs.	Participants will be closely evaluated to monitor for GI AEs.
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. To date, Phase 1 studies in healthy participants and a Phase 1b study in pediatric participants has not shown clinically significant changes in safety laboratory parameters (including	Monitoring will include vital signs, including heart rate, and ECG assessments.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Sisunatovir		
	troponin in C5241001), ECGs and vital signs related to sisunatovir.	

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
Primary:	**Primary:**
• To determine the relative bioavailability of sisunatovir following a single oral dose of CCI mg as PIC vs WGT in a fasted state	• AUC_{last}, AUC_{inf} (if data permit*), and C_{max} of PIC vs WGT
Secondary:	**Secondary:**
• To determine the effect of a high-fat meal on the relative bioavailability of sisunatovir following a single oral dose of CCI mg as WGT	• AUC_{last}, AUC_{inf} (if data permit*), and C_{max} of WGT under fasted vs with a high-fat meal
• To determine the effect of a low-fat meal on the relative bioavailability of sisunatovir following a single oral dose of CCI mg as WGT	• AUC_{last}, AUC_{inf} (if data permit*), and C_{max} of WGT under fasted vs with a low-fat meal
• To characterize the safety and tolerability following a single oral dose of CCI mg of sisunatovir as PIC or WGT in a fasted state, or as WGT in a fed state	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs
Tertiary/Exploratory:	**Tertiary/Exploratory:**

• To determine additional PK parameters of sisunatovir following a single oral dose of CCI mg as PIC or WGT in a fasted state, or as WGT in a fed state	• Additional plasma PK parameters:
	  • CL/F and V_z/F as data permit
	  • T_{max}
	  • $t_{½}$, as data permit

*Should it be deemed that too few AUC_{inf} estimates (eg, less than 10 for a single dose) are obtained from the evaluable participants, AUC_{last} may be selected as the primary/secondary endpoint for CSR reporting (otherwise AUC_{last} will be an exploratory endpoint).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, open-label, 2-part crossover study to evaluate the PK, food effect, safety, and tolerability of sisunatovir CCI mg single dose administered as PIC or WGT under fasted conditions, or as WGT with food.

Part 1

Participants will be admitted to the CRU on Day -1 to undergo baseline procedures. Over the first 2 periods, all participants are planned to receive 1 dose of (A) sisunatovir CCI mg as PIC and 1 dose of (B) sisunatovir CCI mg as WGT in a fasted state. All participants in Period 3 will receive 1 dose of (C) sisunatovir CCI mg as WGT with a high-fat meal (Table 6). There is an at least 72-hour washout period between the dose of 2 adjacent periods.

Part 1 consists of an initial screening period of up to 28 days (while allowing for the return and review of all results, including laboratory tests), a 10-day inpatient stay at the CRU which includes 3 periods, and a follow-up contact that will occur 28-35 days after the last administration of sisunatovir. For individual participants, the total duration of participation from the screening visit to the follow-up visit or phone call will range from approximately 6 weeks (minimum) to approximately 10 weeks (maximum).

Approximately 12 participants will be randomized into 2 sequences with approximately 6 participants in each. For each sequence, participants will receive study interventions in a pre-specified manner as listed in Table 6.

Table 6. Part 1 Treatment Sequence

	Period 1	Period 2	Period 3
Sequence 1 (N=6)	A	B	C
Sequence 2 (N=6)	B	A	C

All study interventions will be administered as a single dose of sisunatovir CCI mg as PIC or WGT.
A= PIC under fasted condition; B = WGT under fasted condition; C= WGT with a high-fat meal.

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

Part 2

Participants will be admitted to the CRU on Day -1 to undergo baseline procedures. All participants are planned to receive 1 dose of (B) sisunatovir CCI mg as WGT in a fasted state and 1 dose of (D) sisunatovir CCI mg as WGT with a low-fat meal. There is an at least 72-hour washout period between the dose of the 2 periods. Participants who have completed Part 1 are eligible to participate in Part 2.

Table 7. Part 2 Treatment Sequence

	Period 1	Period 2
Sequence 1 (N=6)	B	D
Sequence 2 (N=6)	D	B

All study interventions will be administered as a single dose of CCI-mg sisunatovir as WGT.
B = WGT under fasted condition; D= WGT with a low-fat meal.

Part 2 consists of an initial screening period of up to 28 days, a 7-day inpatient stay at the CRU which includes 2 periods, and a follow-up contact that will occur 28-35 days after the last administration of sisunatovir. For individual participants, the total duration of participation from the screening visit to the follow-up visit or phone call will range from approximately 6 weeks (minimum) to approximately 10 weeks (maximum).

Approximately 12 participants will be randomized into 2 sequences with approximately 6 participants in each. For each sequence, participants will receive study interventions in a pre-specified manner as listed in Table 7.

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 relative bioavailability of sisunatovir CCI mg administered under fasted condition as WGT (a formulation intended for future clinical studies) vs PIC (a formulation used in C5241003, C5241005 and C5241006). In addition, food effect will be evaluated for the new WGT formulation. Therefore, it was originally designed to be a 3-period, cross-over study with 72 hours of washout between the dosing in Periods 1 and 2 or Periods 2 and 3.

Based on preliminary PK data from Part 1, a food effect was observed for WGT administered with high-fat meals compared to WGT administered under a fasted state. In order to have a thorough evaluation of the effects of meals on sisunatovir exposure, Part 2 is added to assess the oral PK of sisunatovir administered as WGT with low-fat meals compared to administered as WGT under a fasted state, in a 2-period cross-over design with at least 72 hours of washout between the dosing in Periods 1 and 2. Participants who have participated in Part 1 may also participate in Part 2.

In adults, the half-life of sisunatovir is ~7-10 hours in healthy participants. The effect of formulation on the PK of sisunatovir has been investigated in C5241001 (liquid versus DIC formulation) and C5241005 (PIC [DPB] dispersed in water vs DIC formulation). There is no indication of a change in half-life across formulations. Therefore, current study design with at least 72 hours of washout is supported by the $t_{½}$ (>5× $t_{½}$) between dosing in Periods 1 and 2 or Periods 2 and 3, which is considered adequate.

The effect of food on the PK of a single dose of sisunatovir CCI mg was investigated in C5241001 and C5241005, and appears to be formulation dependent (additional details in Section 2.2.4). As a novel formulation, the effect of food on the PK of sisunatovir administered as WGT will be assessed in this study to inform dose design for future studies.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for sisunatovir, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required for all fertile participants (see Appendix 4).

4.3. Justification for Dose

The dose level used in this study will be CCI mg. Administration of sisunatovir CCI mg as a single dose or multiple doses was demonstrated to be safe and well-tolerated in completed and ongoing clinical studies (eg, C5241001, C5241002, C5241004, C5241005, and C5241006). Higher doses of sisunatovir (C5241001, C5241002) were also demonstrated to be safe and well-tolerated, providing adequate exposure coverage in the event of higher exposures being observed for the new WGT formulation.

Sisunatovir CCI mg was demonstrated to be efficacious in a virus challenge study where sisunatovir at CCI mg CCI × CCI days was as efficacious as CCI mg CCI × CCI days in reducing viral load and total symptom scores; whereas, the CCI -mg dose was associated with GI-related AEs (more details in Section 2.2.4). Thus, CCI mg is the planned Phase 2/3 dose for sisunatovir Phase 2/3 studies in adults. In addition, while CCI mg (the lowest tablet strength) could be considered for this study, due to the observed non-linear PK in completed studies (Section 2.2.4), it is not used in this study as it may not be predictive of CCI mg exposure.

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 or last scheduled procedure shown in the SoA for the last participant in each part.
A participant is considered to have completed the study if the participant have completed all periods of enrolled part(s), including the last visit or the last scheduled procedure shown in the SoA (Table 1 and Table 2).

A participant is considered to have completed the study if they have completed all periods of the enrolled study part(s), 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. If 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, 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. Male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac evaluation.

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

Other Inclusion Criteria:

2. BMI of 16 to 32 kg/m^2; and a total body weight >45 kg (100 lb).

3. Capable of giving signed informed consent as described in Appendix 1, 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.

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions 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 Prior and Concomitant Therapy for additional details).

Prior/Concurrent Clinical Study Experience:

4. 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:

5. A positive urine drug test, confirmed by a repeated test, if deemed necessary.

6. For participants <60 years: Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. For participants ≥60 years old, a screening supine BP of ≥150/90 mm Hg may be used. If systolic BP is ≥ 140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

7. 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.

8. 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 ≥1.05× ULN;
- GGT>1.05× ULN;
- ALP >1.05× ULN;
- Total bilirubin level ≥1.05× 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:

9. 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).
10. History of sensitivity to sisunatovir or any of the formulation components.
11. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day
12. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
13. 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 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

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, approximately 10 hours prior to the dose during Part 1 Periods 1-3 and Part 2 Periods 1-2.

Part 1

- On Dosing Day (Day 1) in Periods 1 and 2, lunch will be the first meal with dosing after an overnight fast of approximately 10 hours. Water is permitted until 1 hour prior to study intervention and may be consumed without restriction beginning 1 hour after dosing.
- On Dosing Day (Day 1) in Period 3, participants will be dosed under high-fat/high-calorie meal condition.
    - Following an overnight fast of approximately 10 hours, participants should start a high-fat/high-calorie breakfast approximately 30 minutes prior to administration of the study intervention. The breakfast will be consumed over approximately 20 minutes with study intervention administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full meal. If participants are unable to complete the entire meal, it will be documented. No food will be allowed for at least 4 hours post-dose.
    - The breakfast will be a high-calorie/high-fat test meal. The test meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively. The following breakfast is a representative example of a high-fat, high-calorie meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 fluid ounces (240 mL) of whole milk.

Part 2

- On Dosing Day (Day 1) for Treatment B, lunch will be the first meal with dosing after an overnight fast of approximately 10 hours. Water is permitted until 1 hour prior to study intervention and may be consumed without restriction beginning 1 hour after dosing.

- On Dosing Day (Day 1) for Treatment D, participants will be dosed under low-fat/low-calorie meal condition.

    - Following an overnight fast of approximately 10 hours, participants should start a low-fat/low-calorie breakfast approximately 30 minutes prior to administration of the study intervention. The breakfast will be consumed over approximately 20 minutes with study intervention administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full meal. If participants are unable to complete the entire meal, it will be documented. No food will be allowed for at least 4 hours post-dose.

    - The breakfast will be a low-calorie/low-fat test meal. The test meal should contain a total calorie of 400-500 Kcal with ~100-125 Kcal (~25%) derived from fat. The following breakfast is a representative example of a low-fat, low-calorie meal: 1 boiled egg, one packet flavored instant oatmeal made with water, and 8 fluid ounces (240 mL) of 1% fat milk.

For all Periods in both Part 1 and Part 2:

- Water can be allowed as desired except for 1 hour after study intervention administration.
- There are no water restrictions prior to dosing for participants dosed under fed conditions.
- Noncaffeinated drinks (except grapefruit or grapefruit -related citrus fruit juices—see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- 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.

- For activity restrictions relating to ECG measurements, see Section 8.3.3.

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 auxiliary 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.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	Sisunatovir
Type	Drug
Use	Experimental
IMP or NIMP/AxMP	IMP

Study Intervention(s)	
Intervention Name	Sisunatovir
Dose Formulation	PIC or WGT
Unit Dose Strength(s)	[redacted] mg for PIC or [redacted] mg for WGT
Dosage Level(s)	[redacted] mg
Route of Administration	Oral
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	The sisunatovir [redacted] mg capsules and [redacted] mg tablets will be provided in bulk. CRU Staff will prepare individual doses for administration.
SRSD	IB
Current/Former Name(s) or Alias(es)	Sisunatovir PF-07923568 RV521

Part 1 Study Arm(s)			
Arm Title	Treatment A	Treatment B	Treatment C
Arm Type	Experimental	Experimental	Experimental
Arm Description	Participants will receive a single [redacted] mg dose of sisunatovir PIC administered orally as [redacted] sisunatovir [redacted] mg capsules under fasted conditions.	Participants will receive a single [redacted] mg dose of sisunatovir WGT administered orally as [redacted] sisunatovir [redacted] mg tablets under fasted conditions.	Participants will receive a single [redacted] mg dose of sisunatovir WGT administered orally as [redacted] sisunatovir [redacted] mg tablets with a high-fat meal.

Part 2 Study Arm(s)		
Arm Title	Treatment B	Treatment D
Arm Type	Experimental	Experimental
Arm Description	Participants will receive a single [redacted] mg dose of sisunatovir WGT administered orally as [redacted] sisunatovir [redacted] mg tablets under fasted conditions.	Participants will receive a single [redacted] mg dose of sisunatovir WGT administered orally as [redacted] sisunatovir [redacted] mg tablets with a low-fat meal.

Sisunatovir will be provided by Pfizer as [CCI]-mg PICs and [CCI]-mg WGTs.

The capsules and tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for time of residence within CRU by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.1.1.1. Part 1

6.1.1.1.1. Periods 1 and 2

Following an overnight fast of approximately 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). 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.

6.1.1.1.2. Period 3

Following an overnight fast of approximately 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) approximately 30 minutes after the start of a high-fat/high-calorie breakfast that will be consumed over approximately 20 minutes. 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. Part 2

6.1.1.2.1. Treatment B

Following an overnight fast of approximately 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer study intervention 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.

6.1.1.2.2. Treatment D

Following an overnight fast of approximately 10 hours, participants will receive study intervention at approximately 0800 hours (±2 hours) approximately 30 minutes after the start of a low-fat breakfast that will be consumed over approximately 20 minutes. 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.

6.2. 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 PCRU local/site 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 PCRU's local/site 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.

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 PICs and WGTs 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). The sisunatovir tablets and capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

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

This is an open-label study.

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 at the site, 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 modification is not allowed for this study.

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 300 mg as single dose or >600 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 follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
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).

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 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. 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.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

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.

Prohibited During the Study

- Medications that can prolong QT or QTc. One resource available to assess whether a drug may prolong QT includes: Home: Crediblemeds (https://crediblemeds.org).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCl) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Follow-up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 6.

If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:
(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 6 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. ECG Changes

A participant who meets either bulleted criterion 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.

7.2. 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.

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 complete 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 in either Part 1 or Part 2, 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.

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.

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 160 mL in Part 1 and approximately 120 mL in Part 2. 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

Efficacy parameters are not evaluated in this study.

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, cardiovascular, and GI 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 record 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 will 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. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. Supine body position with fully lowered headrest should be consistently maintained for each ECG performed.

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.

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 7.

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 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 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6 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. Pregnancy Testing

A urine or 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 starting 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 (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 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 concluded study participation, 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.

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 using the CT SAE Report Form and 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 report 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 report. 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 pre-procedure 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 report 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 report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable

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

Not applicable

8.4.8. Adverse Events of Special Interest

Not applicable

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

Not applicable

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;
- 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, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), 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 0.5 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.

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.

Genetic analyses will not be performed on these plasma samples. 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.

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.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

Retained research samples for genetics are not collected in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

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 summary 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 primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypothesis

There is no statistical hypothesis for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Parameter Set	All randomized participants who receive at least one dose of study medication and in whom at least 1 plasma PK parameter is calculated.
PK Concentration Set	All randomized participants who receive at least 1 dose of study medication and in whom at least 1 plasma concentration value is 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 SAP.

All treatment arms will be reported separately.

9.3.1.1. Derivation of Pharmacokinetic Parameters

PK parameters for sisunatovir will be derived from the concentration-time profiles using noncompartmental methods as data permit. The PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 8. In all cases, actual PK sampling times will be used in the derivation of 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 8. Plasma PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method.
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum observed plasma Concentration	Observed directly from data.
T_{max}	Time to reach C_{max}	Observed directly from data as time of first occurrence.
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$.
V_z/F[a]	Apparent volume of distribution	$Dose/(AUC_{inf} \bullet k_{el})$.

Table 8. Plasma PK Parameters

Parameter	Definition	Method of Determination

a. As data permits.

9.3.2. Primary Endpoint(s) Analysis

Plasma AUC_{last}, AUC_{inf} (if data permit) and C_{max} will be summarized descriptively by treatment. The plasma concentrations of sisunatovir will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

9.3.3. Secondary Endpoint(s) Analysis

9.3.3.1. Safety Analyses

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, 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.

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

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

9.3.3.2. Other Secondary Endpoints Analyses

Part 1

To compare the Treatments A (PIC under fasted condition) and B (WGT under fasted condition), natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of sisunatovir will be analyzed separately using a mixed effect model with sequence (AB or BA), period and treatment included as fixed effects and participant nested within sequence as a random effect. Only data from the first 2 study periods will be used in the analysis. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Treatment A is the Reference treatment and Treatment B is the Test treatment.

For the high-fat food effect evaluation, natural log transformed natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of sisunatovir will be analyzed using a mixed effect model with sequence, and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment B (WGT under fasted condition) is the Reference treatment and Treatment C (WGT with high-fat meal) is the Test treatment. For the food effect comparison only the data from Treatments B and C will be included in the model.

Part 2

For the low-fat food effect evaluation, natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of sisunatovir will be analyzed using a mixed effect model with sequence, and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment B (WGT under fasted condition) is the Reference treatment, Treatment D (WGT with low-fat meal) is the Test treatment.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

The analysis of tertiary/exploratory endpoints will be detailed in the SAP.

9.3.5. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

No interim analysis will be conducted for this study.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve approximately 12 participants randomized to study intervention. The sample size is empirically selected and is not based on statistical power calculation. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator.

The expected widths of the 90% CIs with 80% coverage probability for a range of possible effects (Test vs Reference) are shown in Table 9 below. The calculation assumes a within-participant standard deviations of 0.34 for $\log_e$(AUC) and 0.38 for $\log_e(C_{max})$ based on available Day 1 data of study C5241006.

Table 9. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Relative Effect Estimates at N = 12

Estimated Effect (Test/Reference)	AUC		C_{max}	
	90% CI	CI width	90% CI	CI width
50%	37% to 67%	30%	36% to 69%	33%
75%	56% to 100%	44%	54% to 104%	50%
100%	75% to 134%	59%	72% to 139%	66%
125%	93% to 167%	74%	90% to 173%	83%
150%	112% to 201%	89%	108% to 208%	100%
175%	131% to 234%	104%	126% to 242%	116%
200%	149% to 268%	118%	144% to 277%	133%

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

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. 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.

10.1.4. 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 SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. 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 18 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.

10.1.7. 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 records and 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.

10.1.8. 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 a source document 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 record) 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.

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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 non-study 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. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values; for example: calculation of estimated kidney function (ie, 2021 CKD-EPI eGFR [adults only], as standard lab safety test for FIH and MAD studies). These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 7. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Urea	Local dipstick:	At screening:
Hematocrit	Creatinine	pH	FSH[d]
RBC count	Cystatin C[a]	Glucose (qual)	Urine drug screening[e]
Platelet count	eGFR, eCrCl[b]	Protein (qual)	HBsAg
WBC count	Glucose (fasting)	Blood (qual)	HBsAb
Total neutrophils (Abs)	Calcium	Ketones	HBcAb
Eosinophils (Abs)	Sodium	Nitrites	HCVAb
Monocytes (Abs)	Potassium	Leukocyte esterase	HIV
Basophils (Abs)	Chloride		
Lymphocytes (Abs)	Total CO_2 (bicarbonate)	Laboratory:	Pregnancy test (β-hCG)[f]
	AST, ALT	Microscopy and culture[c]	
	Total bilirubin		
	Alkaline phosphatase		
	Uric acid		
	Albumin		
	Total protein		
	GGT		

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.6.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
d. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
e. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific). Urine drug screening will also be conducted at Admission.
f. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. See SoA for collection times.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and

stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. 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 occurrence in a patient or clinical study participant, 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 abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal 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/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant'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 occurrence 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 start 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 term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward 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" occurred or was necessary, 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 term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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 laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are 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 reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant 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.
- Examples 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 drug dependency or drug 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 reporting SAEs using the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are 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 SAE): is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental 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 Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. 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 reported during 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 usual ADL.

- 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 permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts 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 intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine 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 ruled 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 information, 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 occurred and the investigator has minimal information 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 information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting 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 reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange 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 laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation 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 information 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 information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (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 entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is one of the methods to transmit this information 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 Form 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 Report Form pages within the designated reporting 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 long-term 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 (a) is not pregnant or breastfeeding; (b) agrees to not donate eggs (ova, oocytes) for the purpose of reproduction for at least 28 days after the last dose of the study intervention; and (c) at least 1 of the following conditions applies:

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

  OR

- Is a WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency 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). The

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

OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception 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). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling 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 or oligomenorrhea) 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. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*

    - Intravaginal + barrier*

- Transdermal + barrier*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral + barrier*
   - Injectable + barrier*

8. Sexual Abstinence

   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 options 6 or 7 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: 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."

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, eosinophils (%), 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, total bile acids, 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.

10.6. Appendix 6: Kidney Safety: Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated:

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Table 10.6.2.1.) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

10.6.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)[9]

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

10.6.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate

formulae (see Section 10.6.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units are used for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.6.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria for both pediatric and adult participants.

KDIGO criteria grade (G)	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR ($mL/min/1.73m^2$)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	**A1**	**A2**	**A3**
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.7. Appendix 7: 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). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 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 asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular 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) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-seconds duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is to be reported as AEs/SAEs.

10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below and antibiotics should not be taken with sisunatovir for the period of time at least equal to 5 half-lives plus 14 days preceding the first dose of study intervention, and throughout the conduct of the study. Additionally, precaution should be made to ensure that no concomitant medications that prolong QT or QTc are administered to participants.

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 the 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) if the overall benefit:risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

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

Sisunatovir is a CYP3A4 inhibitor and therefore sensitive and narrow therapeutic index CYP3A4 substrates are also prohibited in this study.

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

Although 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.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

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

CYP3A Inhibitors			
Moderate	**Strong**		
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	Fentanyl		
Sensitive MATE1 Substrates			
Metformin			
P-gp Inhibitors		**P-gp Inducers**	
Atazanavir	Lopinavir	Apalutamide	
Boceprevir	Lumacaftor	Atazanavir	
Cobicistat	Mifepristone	Fosamprenavir	
Conivaptan	Nelfinavir	Lopinavir	

P-gp Inhibitors		P-gp Inducers
Cyclosporine	ombitasvir and paritaprevir and ritonavir and dasabuvir	Rifampin
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		
Not an all-inclusive list.		

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
%CV	coefficient of variation as percentage
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ACR	albumin-to-creatinine ratio
ADL	activity/activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{12}	area under the concentration-time curve from time 0 to 12 hours
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 extrapolated to infinite time
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval tau
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
β-hCG	β-human chorionic gonadotropin
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
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	clearance
C_{last}	the last quantifiable concentration
C_{last}*	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CL/F	apparent clearance
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)

Abbreviation	Term
C-QT	concentration QT
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System
CTMS	Clinical Trial Management System
CYP	cytochrome P450
D#	Day #
DCT	data collection tool
DDI	drug-drug interaction
DF	disoproxil fumarate
DHT	digital health technology
DIC	drug in capsule
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DPB	dry powder blend
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
F	fusion
FIH	first-in-human
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
H_2O	water

Abbreviation	Term
HBcAb	hepatitis B core antibody
HBP	hydroxypropyl
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
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
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
K	Proportionality constant for Schwartz Equations (kidney function)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	terminal phase rate constant
LBBB	left bundle branch block
LFT	liver function test
LRTI	lower respiratory tract infection
MAD	multiple ascending dose
MATE	multidrug and toxic compound extrusion protein
MQI	medically qualified individual
MTD	maximum tolerated dose
NA	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
OCT	organic cation transporter
PCRU	Pfizer Clinical Research Unit
PE	physical examination
P-gp	P-glycoprotein
PIC	Powder in Capsule
PK	pharmacokinetic(s)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time

Abbreviation	Term
Q12h	every 12 hours
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RSV	respiratory syncytial virus
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screat	serum creatinine
Scys	serum cystatin C
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
V_z/F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WGT	Wet Granulation Tablet
WOCBP	woman/women of childbearing potential

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