Title Page

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO- AND POSITIVE-CONTROLLED CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF MULTIPLE DOSES OF SISUNATOVIR ON QTC INTERVAL IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07923568
Study Intervention Name:	Sisunatovir
US IND Number:	143479
[EudraCT/EU CT] Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5241015
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Investigate the Effects of Sisunatovir on QTc Interval in Healthy Adult Participants.

Document History

Document	Version Date
Amendment 1	1 May 2023
Original protocol	16 March 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 (1 May 2023)

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

Section # and Name	Description of Change	Brief Rationale
Document History	Clarify version date of original protocol was approved on 16 March 2023	Version date was not updated as part of approval
1 Synopsis	Updated QTcF of moxifloxacin at 3, 4, or 5 hours on Day 3, updated design that initial planned dose of CCI mg with clarification that dose is adjusted to highest feasible dose to cover high clinical exposure (up to CCI mg), updated statistical methods related to moxifloxacin.	Response to FDA and PCRU feedback
1.3 Schedule of Activities	Added clarification note that HBsAb will be tested if HBsAg and/or HBcAb is positive. Removed Day -1 timepoint since this is done once at screening. Added Prior/concomitant treatments review at ET visit. Added column to clarify that study drug administration on Day 2 occurs at hour 0,not 1.5 hours post-dose.	Clarification from PCRU and aligned with section 10.2 footnote
2.2.3 Nonclinical Safety	Updated safety margins to reflect high clinical exposures of therapeutic dose (200 mg)	Updated to current status of high clinical exposure
2.3.1 Risk Assessment	Removed risk of COVID-19 pandemic	Current status of COVID-19 pandemic.
3 Objectives and endpoints	Updated QTcF of moxifloxacin at 3, 4, and 5 hours on Day 3	Response to FDA feedback
4.2 Scientific Rationale for Study Design	Updated design that initial planned dose of CCI mg with clarification that dose is adjusted to	Response to FDA feedback

Section # and Name	Description of Change	Brief Rationale
	highest feasible dose to cover high clinical exposure (up to CCI mg)	
4.2 Scientific Rationale for Study Design	Added statement and reference that moxifloxacin peak effects on QTcF are delayed when administered with food	Response to FDA feedback
4.2 Scientific Rationale for Study Design	Removed statement of historically observed at 1 to 4 hours postdose	Not relevant to sentence and reference cited
4.3 Justification of Dose	Added justification for CCI under fed conditions and that following review of preliminary data this dose may be increased to CCI mg to ensure coverage of high clinical exposure.	Response to FDA feedback
6.1 Study Intervention(s) and Concomitant Therapy	Updated planned dose to CCI mg with footnote that dose may be adjusted to highest feasible dose (up to CCI mg)	Update based on CCI study results and FDA feedback
6.2 Preparation, Handling, Storage, and Accountability	Removed reference to IPM	As this study is conducted at PCRU, IP manual is not used
6.2.1 Preparation and Dispensing	Removed reference to IPM	As this study is conducted at PCRU, IP manual is not used
6.6 Dose Modification	Updated design that initial planned dose of CCI mg with clarification that dose is adjusted to highest feasible dose to cover high clinical exposure (up to CCI mg)	Response to FDA feedback
8.1 Administrative and Baseline Procedures	Updated total blood volume to 120 mL	clarification
8.5 Pharmacokinetics	Updated Whole blood sample volume for blood/plasma ratio to 2 mL	Feedback from Bioanalytics
9.1.2 Assay Sensitivity	Added text that assay sensitivity of moxifloxacin will be evaluated on Day 3 at 3, 4 and 5 hours post-dose, including post-hoc adjustment and statistical methods.	Response to FDA feedback
9.3.1.2 ECG Data Summaries	Added text that categorization of HR, QRS, and PR intervals will be described in the SAP.	Response to FDA feedback
9.3.3 Secondary Endpoints Analysis	Updated statistical information related to assay sensitivity of moxifloxacin will be evaluated on Day 3 at 3, 4 and 5 hours post-dose.	Response to FDA feedback

Section # and Name	Description of Change	Brief Rationale
10.4.2 Female Participant Reproductive Inclusion Criteria	Clarified that WOCBP agree to use contraception for at least 28 days after last dose of study intervention	The number of days was previously omitted
11 References	Added 2 references related to QTcF peak delays when moxifloxacin is administered under fed conditions	Response to FDA feedback

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Double-blind, Sponsor-Open, Placebo- and Positive-Controlled Crossover Study to Investigate the Effect of Multiple Doses of Sisunatovir on QTc Interval in Healthy Adult Participants

Brief Title: A Study to Investigate the Effects of Sisunatovir on QTc Interval in Healthy Adult Participants.

Regulatory Agency Identification Number(s):

US IND Number:	143479
[EudraCT/EU CT] Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C5241015
Phase:	1

Rationale:

Sisunatovir (PF-07923568) is an orally administered RSV F-protein inhibitor being developed to target viral-host cell fusion for the treatment of adult and pediatric patients with RSV. This study is designed as a thorough QT study (TQT) to assess the effect of sisunatovir on time from the beginning of the QRS complex to the end of the T wave on the electrocardiogram (ECG), corresponding to electrical systole (QT interval) as recommended by the International Council for Harmonisation (ICH) E14 guideline and in Q&As (R3).

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effect on QT interval corrected for heart rate (QTc) interval in healthy participants, of possible clinical therapeutic concentrations of sisunatovir compared with placebo.	• Placebo-corrected, baseline adjusted QTc interval using Fridericia's correction method (QTcF) of sisunatovir at expected maximum concentrations (C_{max}) at the [redacted].
Secondary:	**Secondary:**
• To evaluate the safety and tolerability at possible clinical therapeutic concentrations of sisunatovir, including but not limited to cardiovascular safety.	Adverse event (AE) , ECG assessments, vital sign measurements, and clinical safety laboratory measurements.

Objectives	Endpoints
• To determine study sensitivity by comparing the effect of moxifloxacin 400 mg on QTc interval with placebo at historical moxifloxacin time for maximum observed concentration (T_{max}) of 3-5 hours.	• Baseline adjusted QTcF of moxifloxacin and placebo at T_{max} of 3, 4, or 5 hours on Day 3.

Overall Design:

This is a Phase 1, multiple-dose, randomized, 3-treatment, 3-period crossover, 6-sequence, sponsor-open, placebo- and positive-controlled study to be conducted in approximately 42 adult healthy participants under fed conditions. Approximately 42 participants that will be randomized into 6 sequences with 7 participants in each sequence. Participants assigned to treatment A will receive [redacted] oral doses of sisunatovir administered [redacted] over [redacted] days in a fed state. Participants assigned to treatment B will receive [redacted] oral doses of matching placebo administered [redacted] over [redacted] days in a fed state. Participants assigned to treatment C will receive [redacted] oral doses of placebo administered [redacted] for [redacted] days followed by a single dose of 400 mg moxifloxacin on the morning of Day [redacted]. Treatment assignments to sisunatovir and placebo will be blinded to the participants, investigator and clinical research unit (CRU) staff (except pharmacy and systems staff) but open to the sponsor. Moxifloxacin administration on Day [redacted] will be unblinded.

The sisunatovir dose selected will be the highest feasible sufficiently tolerated dose. In this study, an initial dose of [redacted] has been selected to achieve high clinical exposure based on interpolation between the [redacted] mg and [redacted] mg exposures observed in [redacted]. The safety and PK data from approximately the first 7 participants may be assessed and if observed exposure of [redacted] is lower than predicted (see Table 3) and do not cover the high clinical exposure, then the dose will be increased to [redacted]..

Number of Participants:

Approximately 42 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

Age and Sex:

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

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

Other Inclusion Criteria:

3. BMI of 17.5 to 32 kg/m2; and a total body weight >50 kg (110 lb).

4. Capable of giving signed informed consent.

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).

    - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb. Hepatitis B vaccination is allowed.

    - Positive test result for SARS-CoV-2 infection on Day -1.

2. Participants, who according to the product label for moxifloxacin, would be at increased risk if dosed with moxifloxacin, including but not limited to participants with history of myasthenia gravis, tendinitis/tendon rupture, history of hypersensitivity, allergy, severe adverse drug reaction or intolerance to quinolone antibiotics, including moxifloxacin.

3. Self-reported history or risk factors for QT prolongation or torsades de pointes (eg, organic heart disease, congestive heart failure, hypokalemia, hypomagnesaemia, congenital long QT syndrome, myocardial ischemia or infarction), congenital

deafness, family history of cardiac arrest or sudden death, and family history of long QT syndrome.

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

Prior/Concomitant Therapy:

5. 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 antibiotics and 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.

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

Prior/Concurrent Clinical Study Experience:

7. 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:

8. A positive urine drug test.

9. For females, pregnancy, as indicated by a positive serum pregnancy test at screening and/or positive urine pregnancy test in WOCBP at Day -1.

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

11. 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. Participants with an average QTc interval >450 milliseconds (ms) will not be allowed to participate in the study. Computer interpreted- ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - GFR <60 mL/min/1.73m2 based on CKD-EPI equation;
    - AST or ALT level ≥1.5 x ULN;
    - Gamma-GT >1.2 x ULN;
    - Alkaline phosphatase > 1.2 x ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusion Criteria:

13. 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).
14. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.
15. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
16. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
17. 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.

Study Arms and Duration:

For individual participants, the total duration of participation from the screening visit to the follow-up visit will be approximately 14 weeks. Screening evaluation will occur within the 28 days prior to dosing in the first treatment period. During each treatment period, eligible

participants who meet the entry criteria will be admitted on Day -1, prior to treatment administration on Day 1, and will reside in the PCRU until completion of protocol assessments on Day 4. Participants may be discharged between study periods at the discretion of the investigator. There will be a washout of at least 7 days between dose administrations in consecutive crossover treatment periods. Follow-up contact will be made at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential AEs and concomitant treatments, and to confirm appropriate contraception usage, contact with the participant may be done via phone. For each participant, the duration of participation from Period 1 admission to discharge will be approximately 4 weeks. The follow-up call will occur up to 5 weeks after last dose of study drug .

Study Intervention(s)			
Intervention Name	PF-07923568 (sisunatovir)	Placebo for PF-07923568 (sisunatovir)	Moxifloxacin
Treatment Arm	A	B	C
Unit Dose Strength(s)	50 mg	Placebo	400 mg
Dose Formulation	Capsule	Capsule	Tablet
Dosage Level(s)	Planned doses are CCI* mg CCI for [redacted] doses	0 mg CCI for [redacted] doses	400 mg moxifloxacin on Day [redacted]**
Route of Administration	Oral	Oral	Oral
Use	Experimental	Placebo-comparator	Active-comparator
IMP or NIMP/AxMP	IMP	IMP	AxMP

* Dose will be adjusted to the highest feasible dose that is sufficient well tolerated, up to CCI .

** Sisunatovir placebo will be administered CCI for [redacted] doses, followed by a single dose of 400 mg moxifloxacin on Day [redacted].

Statistical Methods:

In this study approximately 42 participants will be enrolled. Statistical power analyses suggest that 42 participants will provide approximately 99% power to detect a mean difference of 5 msec between moxifloxacin and placebo at 3 hours post-dose of moxifloxacin (historic population T_{max}) if the expected mean difference between moxifloxacin and placebo is no less than 10 msec at T_{max}.

For the primary objective, a PK/pharmacodynamic (PD) model will be established to characterize the relationship between sisunatovir plasma concentration and change from baseline in heart rate-corrected QT interval (ΔQTc) in this study. Change from baseline in Fridericia's heart-rate corrected QT interval (ΔQTcF) will be the default dependent variable.

The model-derived mean placebo-corrected change from baseline in QTc (ΔΔQTcF) and corresponding 2-sided 90% confidence intervals (CIs) will be computed at concentrations of interests, eg, expected C_{max} at the [redacted]. If the upper bound of the 2-sided 90% interval for the ΔΔQTcF as estimated by the final concentration-ΔQTc model established in this study is <10 msec at the highest clinically relevant exposure, the absence of an effect of sisunatovir on QTc will be concluded. The highest clinically relevant exposure (due to intrinsic and/or extrinsic factors) will be determined later from other studies.

For the secondary objective to determine study sensitivity, the change from baseline QTcF interval will be analyzed using a MMRM model with sequence, period, treatment, time (post-dose timepoint), and treatment by time interaction as fixed effects, participants as random effect, and baseline QTcF as covariate. Estimates of the mean difference between moxifloxacin and placebo at 3, 4, and 5 hrs post-dose and the corresponding two-sided Bonferroni-adjusted 90% CIs (96.7% CIs) will be reported separately. This study will be deemed sensitive to detect QT/QTc prolongation if the lower limit of the Bonferroni-adjusted 90% CI (96.7% CI) of mean difference between moxifloxacin and placebo at any of the 3, 4, or 5 hrs post-dose is greater than 5 msec.

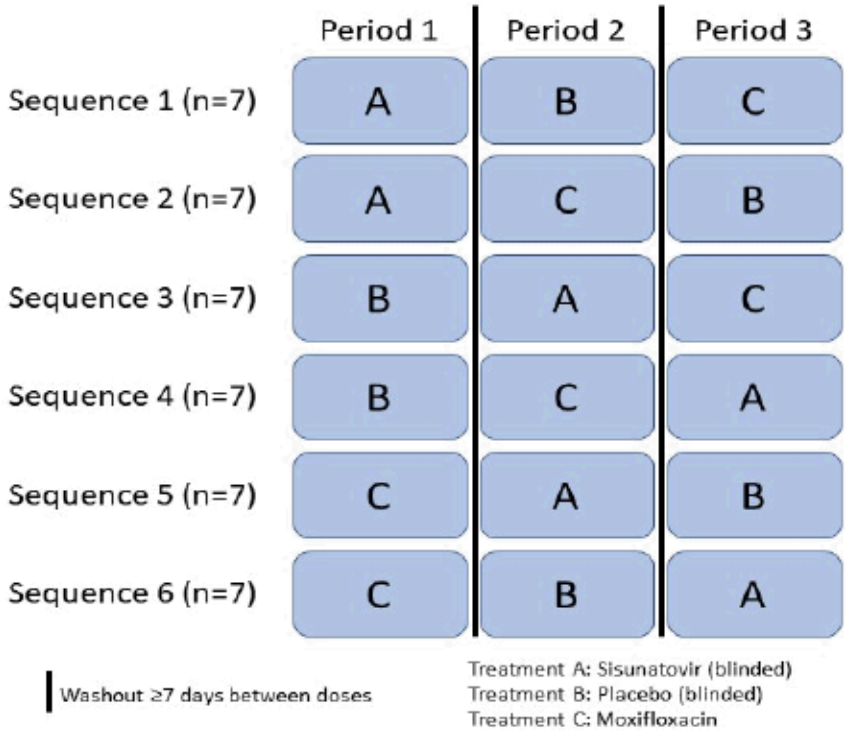
Ethical Considerations:

There is no known benefit for healthy participants participating in this trial. This study is designed primarily to investigate the effects of sisunatovir on QTc Interval.

Based on the data from completed Phase 1 and 2 studies, the clinical safety profile of sisunatovir appears to be acceptable. Sisunatovir will be administered in this study at doses that were found to be well tolerated in previous studies.

Moxifloxacin is a fluoroquinolone antibiotic that produces consistent and predictable QT prolongation and a single dose of 400 mg is routinely used as a positive control in Concentration QT/QTc (C-QT) studies.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed 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

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screen	Period 1 to Period 3																F/U Call	ET	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**						**Day 3**								**Day 4**	**31-38 Days**		• Screening ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • Washout ≥7 days between doses
Hours After Dose				**0**	**1.5**	**4**	**5**	**6**	**12**	**0**	**1.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**			
Informed consent	X																				• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.2 for additional information.
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			
Inclusion/exclusion criteria	X	X																			• Period 1 only
Medical/medication history	X	X																	X		• Period 1 only
Prior/concomitant treatments	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	• Review concomitant treatments
Physical exam	X	X																X		X	• PE at Screening or Period 1 Day -1 only. A brief PE at other times at the discretion of the investigator. • Including height and weight at screening only.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screen	Period 1 to Period 3																	F/U Call	ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2						Day 3								Day 4	31-38 Days		• Screening ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • Washout ≥7 days between doses
Hours After Dose				0	1.5	4	5	6	12	0	1.5	3	4	5	6	8	12	24			
Safety laboratory	X	X		X														X		X	• Participants should fast for at least 4 hours before safety labs are drawn. • Includes urinalysis.
Demography	X																				
Pregnancy test (WOCBP only)	X	X																		X	• Day -1 pregnancy testing in Period 2 and 3 only if participant is discharged from CRU between periods. • ET pregnancy testing only if participant withdraws while not admitted to the CRU.
Contraception check	X	X																X	X	X	
FSH (post-menopausal women only)	X																				
Urine drug testing	X	X																			• Day -1 urine drug testing in Period 2 and 3 only if participant is discharged from CRU between periods.
12-Lead ECG (*triplicate*)	X		X								X	X	X	X	X	X	X	X		X	• Refer to Section 8.4.4 • Single ECG for Screening. • Pre-dose ECGs are 3 sets of triplicates approximately 40 min, 25 min, and 10 min before pre-dose meal. • All other ECGs are triplicate.
Vital Signs (BP, PR)	X		X							X		X			X			X		X	

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Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2						Day 3								Day 4	31-38 Days		• Screening ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • Washout ≥7 days between doses
Hours After Dose				0	1.5	4	5	6	12	0	1.5	3	4	5	6	8	12	24			
HIV, HBsAg, HBsAb, HBcAB, HCVAb	X																				• HBsAb will be tested if HBsAg and/or HBcAb is positive
COVID-19 related procedures	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		X	• Performed per local procedures.
Study intervention administration			X	X						X											• For sisunatovir and placebo: CCI on Day 1-2, on Day [redacted] only in the morning dose will be administered • For moxifloxacin: placebo CCI on Days 1-2, on Day [redacted] only in the morning moxifloxacin will be administered. Moxifloxacin administration on Day [redacted] is unblinded. • The washout between last dose in previous period ≥7 days (Periods 2 and 3 only). • Dosed in the fed state.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screen	Period 1 to Period 3																	F/U Call	ET	Notes
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2						Day 3								Day 4	31-38 Days		• Screening ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • Washout ≥7 days between doses
Hours After Dose				0	1.5	4	5	6	12	0	1.5	3	4	5	6	8	12	24			
Pharmacokinetic blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	• Time 0 PK sample must be collected prior to dose administration. • Blood samples will be collected following the 0 hour and post-dose ECG measurements at the same time-points for Treatment A, B, and C • Day 2 PK samples collected in Period 1 only.
Pharmacokinetic microsampling (Tasso®)					X	X	X	X	X												• Day 2 PK microsamples collected in Period 1 only. Time-matched to PK blood sampling
Blood/Plasma ratio sampling							X		X												• Day 2 whole blood samples collected in Period 1, 2 and 3 to generate a whole blood and a plasma sample.
CRU discharge																		X			• Discharge permitted on Day 4 in each period or only at Day 4 of period 3 at the discretion of the investigator.
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	• See Section 8.5.3 for follow-up AE and SAE assessments.

2. INTRODUCTION

PF-07923568 (sisunatovir, formerly RV521) is an orally administered RSV F-protein inhibitor being developed to target viral-host cell fusion for the treatment of adult and pediatric patients with RSV.

2.1. Study Rationale

The purpose of the study is to investigate the effects of multiple oral doses of sisunatovir on QTc Interval.

2.2. Background

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

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

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

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

This study is designed to assess the effect of sisunatovir on time from ECG Q wave to the end of the T wave corresponding to electrical systole (QT interval) as recommended by the ICH E14 guideline and in ICH E14 Q&As (R3).[7] The concentration-QT analysis is defined as the primary analysis in this study and serves as the primary basis for the decision to classify the QT prolongation risk for sisunatovir.

2.2.1. Nonclinical Pharmacology

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

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

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

- Refer to the sisunatovir IB for further details.

- Sisunatovir was shown to be an inhibitor of the hERG channel in a GLP study (IC50 = 1.8 µM). Subsequent non-GLP studies have shown that sisunatovir is also an inhibitor of other ion channel subtypes including the calcium channel Cav1.2 (IC50 = 19.8 µM) and the cardiac sodium channel Nav1.5 (IC50 = 12.1 µM). It is known that activity at both of these ion channel subtypes can potentially offset the delayed repolarization of the cardiac action potential that results from hERG inhibition.

- Sisunatovir was assessed in a hIPSC-CM model (unpaced: intrinsically beating cells) to determine if it would produce an increase in APD_{90} or $ycAPD_{90}$ following both acute (30 min) and chronic (24 h) exposure to the drug. This system has been shown to be predictive of drug-induced increases in clinical QTc, with the highest predictivity observed using the chronic 24 h timepoint. Under acute treatment conditions sisunatovir produced an increase in the $ycAPD_{90}$ endpoint that would predict a 10msec increase in QTc in the clinic at a free concentration of 1.8 µM, 5.5-fold higher than the expected High Clinical Exposures for 200 mg Q12 x 5 days, respectively. The mean response for the non-rate corrected data at 30 minutes did not reach a threshold effect, however the standard deviation of the mean did reach the threshold at the 4 µM test concentration. This threshold concentration would predict a 10msec increase in QTc in the clinic at a free concentration of 2.9 µM (>8.9-fold the High Clinical Exposure of 200 mg Q12). Under chronic treatment conditions in the stem cell cardiomyocytes sisunatovir did not produce an increase in either APD_{90} or $ycAPD_{90}$ at any of the concentrations tested (up to 100 µM).

- In addition to assessing sisunatovir in a stem cell model, ion channel data was modeled (hERG binding, Cav1.2/Nav1.5 patch clamp) to define arrhythmia risk, specifically TdP using an in-silico model. Analysis suggested a threshold free exposure of ≥1.4 µM would be associated with a TdP class probability risk of >0.5. This is 4.3-fold higher than the expected High Clinical Exposures for 200 mg.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

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

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

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

- *In vitro* studies indicate a DDI risk exists for CCI. However, ratios of unbound hepatic inlet concentrations relative to Ki values are low, and DDI risk is considered unlikely for CCI. The pharmacokinetics of CCI substrates may be altered when co-administered with sisunatovir, and therefore sensitive CCI substrates are prohibited in this protocol (Appendix 9).

- *In vitro* studies indicate there is a risk of inhibition of CYPs CCI. The DDI with CYPs CCI is predicted to be minimal (predicted less than 25% increase in AUC of a sensitive substrate) and DDI with CCI is predicted to be weak. A DDI study conducted with sisunatovir (200 mg Q12) and midazolam as a sensitive CYP3A4 probe substrate (C5241004) indicate that sisunatovir is a moderate 3A4 inhibitor. There is also a possibility that the pharmacokinetics of CCI substrates may be altered when coadministered with sisunatovir. Based on these findings sensitive or narrow therapeutic index 3A4 substrates and narrow TI CCI substrates are prohibited in this protocol (Appendix 9).

- *In vitro* studies indicate that sisunatovir is a P-gp substrate; therefore, co-administration of inhibitors for the transporter (P-gp) may result in increased exposure to sisunatovir (approximately 2-fold). A clinical DDI study (C5241004) indicated that verapamil (a P-gp and CYP3A4 inhibitor) coadministration produced an approximately 2.5-fold increase in exposure to sisunatovir. Based on these findings, strong and moderate CYP3A4 and P-gp inhibitors or inducers are prohibited in this protocol (Appendix 9).

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

levels. Confirmation of major metabolites produced in humans is currently underway in an ADME study, pending results of metabolite identification (C5241008).

2.2.3. Nonclinical Safety

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

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

- In anesthetized guinea pigs, there were no effects on the QT or QTc (QTcB and QTcF) interval at any dose following intravenous administration (successive dose of 1, 3, and 10 mg/kg). At the highest dose, where peak exposure to free sisunatovir was approximately 735 ng/mL (~4.7-fold the High Clinical Exposure of 200 mg Q12 x 5 days), a slight reduction in HR together with elevated arterial blood pressure, LVSP, LV +dP/dtmax (and dP/dtmax), RR, PR and QRS interval were observed compared to vehicle.

- In conscious telemetered dogs, oral doses of sisunatovir up to 120 mg/kg were evaluated for effects on BP, HR, lead II ECG (PQ, QT, QTc interval [QTcB and QTcV], QRS duration, and ECG waveform morphology), and body temperature. Changes in cardiovascular parameters were limited to a transient increase in HR noted from 12 to 16 hours postdose at ≥45 mg/kg with no concomitant changes in QT

or QTc interval and a slight increase in diastolic arterial pressure observed up to 12 hours postdose at ≥45 mg/kg. At 120 mg/kg, decreases in PQ interval were observed at 2 hours postdose in the absence of noticeable changes in any other ECG parameter. These values remained within the normal range in conscious dogs. Exposure estimates are based on another study, in which a single dose of 120 mg/kg in male dogs had a free C_{max} of approximately 489 ng/mL (~3.1-fold the High Clinical Exposure of 200 mg Q12 x 5 days).

- Juvenile dogs dosed up 45 mg/kg QD for 3 weeks showed no effects on cardiovascular parameters (free C_{max} of 399 ng/mL). Dogs dosed up to 120 mg/kg QD for 14 days showed no effects on cardiovascular parameters (free C_{max} of 707 ng/mL; ~4.5-fold the High Clinical Exposure of 200 mg Q12 x 5 days). Dogs dosed up to 15 mg/kg QD for 28 days showed no test article related effects on ECG parameters. At 45 mg/kg/day decreases in group mean HR and increases in RR, PR, QT, and QTcV interval were noted, although individual values were within the normal range for animals of this age. It should be noted that the observed increase in QTcV interval in females was likely due to a notable increase of approximately 20-30 msec from predose in two females.

2.2.4. Clinical Overview

Table 2. Completed sisunatovir Studies

Study Number (Status)	Study Type / Key Design Features	Study Population	Dose, Dosing Regimen	Formulation Used
C5241001 (previously REVC001[a]) (completed)	Phase 1, randomised, double-blind, placebo-controlled, safety, tolerability, PK, food-effect of SAD and MAD	Healthy participants	Dose range: 10 mg – [CCI] mg (SAD); 36 participants Dose range: 175 mg – [CCI] mg; Q12 (MAD), Food effect; 24 participants	Liquid Formulation DIC
C5241002 (previously REVC002) (completed)	Phase 2a, randomised, double-blind, placebo-controlled	Healthy participants inoculated with RSV CV	200 mg or 350 mg Q12 for a total 10 doses; 66 Participants	DIC
C5241004 (previously REVC004) (completed)	Phase 1, adaptive, part randomised, part open-label, drug interactions, safety, tolerability	Healthy participants	200 mg; Q12; 62 Participants	DIC

Table 2. Completed sisunatovir Studies

Study Number (Status)	Study Type / Key Design Features	Study Population	Dose, Dosing Regimen	Formulation Used
C5241005 (previously REVC005) (completed)	Phase 1, open-label, single-dose, PK, safety, and tolerability study	Healthy participants	200 mg, 4 single doses total; 9 Participants 1 ×: DIC (fed) 1 ×: DPB dispersed in H2O (fed) 1 ×: DPB dispersed in H2O (fasted) [wash-out: 3 days between each of the 3 dosing days]	DIC DPB

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

A total of 201 adult healthy participants have received sisunatovir in 4 completed clinical studies (C5241001, C5241002, C5241004 and C5241005) investigating the PK profile, effects of food on PK, effects of formulation on PK (C5241001, C5241005), DDIs (C5241004), and the efficacy in an RSV Viral Challenge Study (C5241002) at doses ranging from 10 mg to 525 mg. In addition, as of 03 October 2022, 45 pediatric patients hospitalized due to RSV LRTI have been enrolled into the ongoing C5241003 study.

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

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

In adults, under both fasting and fed conditions sisunatovir is slowly absorbed reaching maximum plasma concentrations (t_{max}) at 5-6 hours (hrs) with a relatively moderate

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

The effect of food on the single dose pharmacokinetics was assessed for the DIC and DPB dispersed in water. For the DIC the extent of systemic exposure to sisunatovir (geometric mean AUC_{inf} under fed and fasted conditions) was 357 and 221 ng.h/mL respectively, with the between-subject variability being lower under fed conditions (CV 64.1% compared with 198%). The ratio of fed/fasted was 218% (90% CI 94.2 - 502%) for C_{max} and 162% (90% CI 83.0 – 316%) for $AUC_{0\text{-}inf}$. It should be noted that the DIC fasted results from C5241001 were lower than typically seen in other studies with 200 mg administered under fasting conditions, resulting in an artificially higher ratio of fed/fasted in this study. For the DPB dispersed in water the extent of systemic exposure to sisunatovir (geometric mean $AUC_{0\text{-}inf}$) under fed and fasted conditions was 371 and 337 ng.h/mL respectively, with the between-subject variability being slightly lower under fasted conditions (CV 49.0% compared with 61.6%). The ratio of fed/fasted was 107.7% (90% CI 78.0 – 148.8%) for C_{max} and 110.0% (90% CI 85.6 – 141.4%) for $AUC_{0\text{-}inf}$.

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

In an RSV challenge study, sisunatovir treatment resulted in a statistically significant reduction in AUC of RSV viral load compared with placebo; 55.25% (p=0.007) and 63.05% (p=0.002) for the 200 mg and 350 mg sisunatovir dose groups respectively (dosed Q12 hours for 5 days). Results for the AUC of total symptom score were consistent with the viral load AUC. Geometric mean AUCs of total symptom score were 195.56, 30.79 and 31.76 hours for placebo, 200 mg sisunatovir and 350 mg sisunatovir, respectively. The reduction in AUCs of total symptom score compared with placebo was statistically significant for both sisunatovir treatment groups; p=0.009 (84.26%) and p=0.002 (83.76%), (Wilcoxon Rank-Sum test) for the 200 mg and 350 mg sisunatovir dose groups, respectively.

No significant QTc prolongation was detected in C-QT analyses performed in SAD participants (C5241001), MAD participants (C5241001), or DDI study participants (C5241004).

SAD portion of C5241001: Overall, the modeling predictions suggest a shortening of QTcF with increased dose, if any effect at all. This is supported by the "by timepoint" analysis that does not show any dose related effects. This study did not include a placebo group, but since the lowest dose (10 mg) resulted in exposure below the limit of detection, the data from this group was used as a surrogate for placebo.

MAD portion of C5241001: The results show no indication that RV521 prolongs the QT interval – the slope for the concentration effect for RV521 is numerically small and significantly negative. In fact, the findings correspond well with those based on Part A.

C5241004: This study was designed as a drug-drug interaction study with pharmacokinetic primary endpoints and a secondary endpoint to compare paired PK and QTc interval parameters pre-dose to post-dose of sisunatovir. There were no clinically significant changes in ECG mean heart rate, QRS duration, QRS axis, QT interval, QTcF interval, QTcB interval, or RR interval. Concentration-effect modelling was performed to assess sisunatovir's effect on QTcF and the PR interval; this revealed no concern of clinical or regulatory relevance regarding a QT- or PR-prolonging effect of sisunatovir , neither as monotherapies nor in combination. This result gets further weight by the uniformity across the models and analyses sets investigated and by the presence of a strong effect of breakfast which was used to show assay sensitivity.

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

There is no known benefit for healthy participants participating in this trial. This study is designed primarily to investigate the effects of sisunatovir on QTc Interval.

For healthy participants participating in this study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of sisunatovir as a potential new, pharmacological agent for the treatment of RSV. As of 14 September 2022, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.1. The clinical impact of these potential risks will be minimized through standard, intensive, inpatient monitoring of the participants following administration of multiple oral doses of the study intervention. Based on the data from Phase 1 and 2 studies, the clinical safety profile of sisunatovir appears to be acceptable at mean (%CV) CCI up to CCI (CCI %) ng/mL and mean (%CV) CCI up to CCI (CCI %). 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.

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, including SRSDs for required AxMPs, for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) sisunatovir		
Hepatobiliary system effects	Degenerative and inflammatory changes in the bile duct of both rats (≥ 60 mg/kg/day) and dogs (≥45 mg/kg/day) in studies of up to 28 days, with elevated plasma levels of ALP, ALT and GGT in dogs only. Evidence of recovery for all findings following a 14-day treatment-free period	Standard monitoring including laboratory (i.e., transaminases, ALP, GGT) and AE monitoring.
Gastrointestinal effects	Transient dose-related incidence of emesis and liquid faeces in dogs at doses ≥15 mg/kg/day in studies up to 28 days. Additionally, inflammation in duodenum, gallbladder, and liver at 45 mg/kg/day noted in 28-day dog study. In previous clinical studies sisunatovir has been associated with mild GI AEs.	As this is an investigational agent, there is some risk that is mitigated by close observation of AEs, etc. Participants will be closely evaluated in an in-patient setting to monitor for GI AEs. If needed, palliative alleviating measures such as antiemetics may be provided.
Renal effects	Degeneration/regeneration of medullary tubules was noted in rats at ≥120 mg/kg/day in studies of up to 28 days; considered non-adverse based on lack of clinical pathology changes.	Standard monitoring including laboratory and AE monitoring.
Cardiovascular effects	Myocardial degeneration and necrosis was noted at 240 mg/kg/day (non-tolerated dose) in a 14-day rat study. No similar effect in rats at 120 mg/kg/day in the 28-day study, or in dogs at any dose, for 14 or 28 days.	Monitoring will include vital signs, including heart rate, and ECG assessments.
Pulmonary effects	Vascular degeneration/necrosis in lung at 240 mg/kg/day and epithelial degeneration/necrosis in trachea at 120 mg/kg/day in 14-day rat study.	There will be standard safety monitoring including vital signs and adverse events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No similar effect in rats at 120 mg/kg/day in the 28-day study, or in dogs at any dose, for 14 or 28 days. Phase 1 FIH study (C5241001) showed no adverse clinically significant changes in safety laboratory parameters (including troponin), ECGs and vital signs.	
Thymus effects	Lymphoid atrophy and decreased thymus weight and reduced size of thymus in both rats (≥ 120 mg/kg/day) and dogs ≥15 mg/kg/day) in studies of up to 28 days. Evidence of recovery following a 14-day treatment-free period. These findings are secondary to stress and not directly sisunatovir related	Standard monitoring including laboratory (i.e., complete blood count with differential) and AE monitoring. Brief 3-day course regimen should further limit this potential risk.
Study Intervention(s) moxifloxacin		
Gastrointestinal disturbances (eg, nausea, diarrhoea, vomiting)	Adverse reactions reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for AEs in an inpatient clinical research unit.
Hypersensitivity reactions, including anaphylactic reactions	Adverse reactions reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored by vitals and for AEs in an inpatient clinical research unit. Participants with history of hypersensitivity or intolerance to quinolone antibiotics, including moxifloxacin, will be excluded.
Peripheral neuropathy, exacerbation of myasthenia gravis, and central nervous system effects including agitation, insomnia, dizziness and anxiety.	Adverse reactions reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for AEs in an inpatient clinical research unit. Participants with history of myasthenia gravis are excluded.
Tendinitis and tendon rupture	Adverse reaction reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		for AEs in an inpatient clinical research unit.
Prolongation of the QT interval and isolated cases of torsade de pointe	Adverse reaction reported following moxifloxacin administration	A single dose of 400 mg will be administered in the study. Participants will be monitored for cardiac changes (telemetry and ECG) and AEs in an inpatient clinical research unit. Participants with known history or risk factors for prolonged QT will be excluded.

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 evaluate the effect on QT interval corrected for heart rate (QTc) interval in healthy participants, of possible clinical therapeutic concentrations of sisunatovir compared with placebo.	• Placebo-corrected, baseline adjusted QTc interval using Fridericia's correction method (QTcF) of sisunatovir at expected maximum concentrations (Cmax) at the CCI [redacted].
Secondary:	**Secondary:**
• To evaluate the safety and tolerability at possible clinical therapeutic concentrations of sisunatovir, including but not limited to cardiovascular safety.	• Adverse event (AE) , ECG assessments, vital sign measurements, and clinical safety laboratory measurements.
• To determine study sensitivity by comparing the effect of moxifloxacin 400 mg on QTc interval with placebo at historical moxifloxacin time for maximum observed concentration (T_{max}) of 3-5 hours.	• Baseline adjusted QTcF of moxifloxacin and placebo at T_{max} of 3, 4, and 5 hours on Day 3.
Exploratory:	**Exploratory:**
• To evaluate the effect of sisunatovir on the electrocardiogram (ECG) parameters of, heart rate, PR interval and QRS interval.	• Baseline adjusted heart rate, PR interval, and QRS intervals of sisunatovir and placebo at each postdose time point.
• To evaluate the plasma pharmacokinetics (PK) of sisunatovir following multiple oral doses.	• Plasma sisunatovir parameters, including C_{max}, T_{max} and area under the plasma concentration-time profile from time 0 to 24 hours (AUC_{24}) post-dose on Day 3.
• To explore PK of sisunatovir by microsampling technique.	• Concentration of sisunatovir from paired samples obtained via microsampling compared to venous sampling.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, multiple-dose, randomized, 3-treatment, 3-period cross-over, 6-sequence, sponsor-open, placebo-and positive-controlled study to be conducted in approximately 42 adult healthy participants under fed conditions. Approximately 42 participants will be randomized into 6 sequences with 7 participants in each sequence. Participants assigned to treatment A will receive [redacted] oral doses of sisunatovir administered CCI [redacted] over [redacted] days in a

fed state. Participants assigned to treatment B will receive [redacted] oral doses of matching placebo administered [redacted] over [redacted] days in a fed state. Participants assigned to treatment C will receive [redacted] oral doses of placebo administered [redacted] for [redacted] days followed by a single dose of 400 mg moxifloxacin on the morning of Day [redacted]. Treatment assignments to sisunatovir and placebo will be blinded to the participants, investigator and CRU staff (except pharmacy staff) but open to the sponsor. Moxifloxacin administration on Day [redacted] will be unblinded.

For individual participants, the total duration of participation from the screening visit to the follow-up visit will be approximately 14 weeks. Screening evaluation will occur within the 28 days prior to dosing in the first treatment period. During each treatment period, eligible participants who meet the entry criteria will be admitted on Day -1, prior to treatment administration on Day 1, and will reside in the PCRU until completion of protocol assessments on Day 4. Participants may be discharged between study periods at the discretion of the investigator. There will be a washout of at least 7 days between dose administrations in consecutive crossover treatment periods. Follow-up contact will be made at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential AEs and concomitant treatments, and to confirm appropriate contraception usage. Contact with the participant may be done via phone. For each participant, the duration of participation from Period 1 admission to dishcharge will be approximately 4 weeks. The follow-up call will occur up to 5 weeks after last dose of study drug.

4.2. Scientific Rationale for Study Design

This purpose of this study is to assess the effect of sisunatovir on QT interval as recommended by the ICH E14 guideline and in ICH E14 Q&As (R3).[7] The concentration-QT analysis is defined as the primary analysis in this study and serves as the primary basis for the decision to classify the QT prolongation risk for sisunatovir.

Preliminary [redacted] analysis of SAD and MAD data (C5241001) for sisunatovir suggested that overall, the model predicts [redacted] doses of up to [redacted] mg and [redacted] doses of up to [redacted] mg of RV521 with [redacted] on ECG parameters. The effects of sisunatovir on QT interval was evaluated in Part A (single dose administration) of the study. This part of the study did not include a placebo group, but since the lowest dose (10 mg) resulted in exposure below the limit of detection, the data from this group was used as a surrogate for placebo. A model was built to investigate the effect of RV521 on QTcF at concentrations seen in Part A of the study. In particular, predictions of the effect at the geometric mean of the individual C_{max} values under each dose with quantifiable concentration and at least 6 participants were given together with two-sided 90% confidence intervals. As the results [redacted] any effect of RV521 on [redacted], and, indeed indicate no effect at all, a more in-depth investigation into the appropriateness of the assumption of linearity or absence of PK-PD-hysteresis was not considered necessary. A similar evaluation was performed for data obtained from Part B (placebo controlled, multiple dose administration) and a similar conclusion was reached where no effect of treatment on QTcF was observed.

In order to achieve therapeutic concentrations the current study will dose to steady state, which is achieved after approximately [redacted] so the current study will evaluate

QTc interval at steady state on Day 3. As the exposure of sisunatovir increases in a greater than dose proportional manner, the current study will evaluate the highest feasible dose that is projected to be well tolerated. In this study, an initial dose of CCI has been selected to achieve high clinical exposure based on interpolation between the CCI mg and CCI mg exposures observed in CCI. The safety and PK data from approximately the first 7 participants may be assessed and if observed exposure of CCI is lower than predicted (see Table 3) and does not cover the high clinical exposure, then the dose will be increased to CCI.

The effect of food on the pharmacokinetics of sisunatovir has been variable in Phase 1 studies. However, the effect of food on the pharmacokinetics of sisunatovir using the formulation to be used in this study (dry powder blend in capsules) showed minimal food effect. The current study will administer study intervention under fed conditions. The impact of food on ECG measurements will be controlled by consistent timing and content of meals across sisunatovir, placebo, and moxifloxacin treatments.

A concurrent placebo control will be included in accordance with ICH E14 recommendations to enhance the validity of this study and to avoid potential biases associated with study procedures.

To increase the confidence that this study has the ability to detect a QTc prolongation in the range of approximately 5 ms, a concurrent positive control will be included to establish assay sensitivity. In this study, moxifloxacin will be used as the active control. Moxifloxacin is a fluoroquinolone antibiotic that produces consistent and predictable QT prolongation and is routinely used as a positive control in TQT studies. Based on recent Pfizer experience from TQT trials conducted at internal CRUs using automated readings, a single 400 mg dose of moxifloxacin produces a maximum mean heart rate-corrected QT interval using Fridericia's correction (QTcF) change from baseline between 7.9 msec and 11.0 msec 2 to 5 hours postdose time points with machine readings. The t_{max} of moxifloxacin is delayed by ≥1 hour when administered under fed conditions[8,9], with delays in the peak effects on QTc to 4 hours post-dose[9]. Encapsulation of commercially available moxifloxacin tablets to achieve blinding has the potential to have an impact on absorption, therefore encapsulation will not be employed and moxifloxacin will be administered on Day 3 in an open manner. Blood samples from participants randomized to placebo or moxifloxacin will be collected and retained, but will not be routinely analyzed.

All ECG measurements will be performed in triplicate at each nominal sampling time (see Schedule of Activities and Electrocardiogram Section 8.3.3). Triplicate measurements are intended to reduce the intrinsic variability and measurement error associated with ECG measurement of the QT/QTc interval. The collection of ECGs at multiple time points is performed to take into consideration the diurnal pattern and variability of QT intervals, dependent upon multiple factors including activity level, postural changes, circadian patterns and food ingestion. The sampling time points have been chosen based on the expected PK profiles of sisunatovir and moxifloxacin. The time to reach maximum concentration (T_{max}) for sisunatovir is approximately 4 to 6 hour postdose based on previous Phase 1 and 2 studies

(Summary of sisunatovir Pharmacokinetics Section 8.5). This schedule will also allow peak QT effects with moxifloxacin, to be captured.[7]

To minimize the risks of COVID-19 related complications to participants and the study site personnel, assessment of risk for, symptoms of or testing for COVID- 19 may be performed at screening, admission to the CRU, and/or at other times during the study at investigator discretion and according to local site policies.

As this is healthy participant study, the use of concomitant medications in this study is expected to be minimal. Nevertheless, according to the DDI risk assessment for sisunatovir as described in Section 2.2.2, sisunatovir is a moderate inhibitor of CYP3A4 and is projected to be a weak inhibitor of CCI. For this reason sensitive and narrow TI CYP3A4 substrates and sensitive and narrow TI CCI substrates are prohibited in this study. Since sisunatovir is a P-gp and CYP3A4 substrate, strong and moderate CYP3A4 and P-gp inhibitors or inducers are prohibited. Lastly, due to risk of CCI and CCI inhibition, sensitive substrates of these transporters are prohibited. Use of specific prohibited prior/concomitant therapies are outlined in Appendix 9.

4.2.1. Choice of Contraception/Barrier Requirements

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

4.3. Justification for Dose

Considering the exposure of sisunatovir increases in a greater than dose proportional manner, the current study will evaluate the highest feasible dose that is well tolerated. The pharmacokinetics of CCI mg and CCI mg Q12 hour doses have been evaluated in study CCI with the same formulation that is to be used in this study (draft PK data available, final reporting pending). Draft results from CCI indicate that the CCI mg Q12hr sisunatovir dose under fed conditions resulted in mean exposure above rat NOAEL associated with the 28-day GLP study, whereas exposures associated with 200 mg Q12hr were consistent with those observed in previous Phase 1 studies with sisunatovir, including the human challenge study (C5241002). As of 4 April 2023, in study CCI there have been no SAEs attributable to sisunatovir and no study drug discontinuation due to an AE. The most common AEs are GI related (nausea, diarrhea, abdominal pain/distention), consistent with previous studies. No clinically meaningful trends were seen with ECG parameters, vital signs or laboratory values.

In this study, an initial dose of CCI has been selected. Table 3 shows the anticipated mean steady-state exposure at the Phase 2/3 clinical dose (200 mg Q12hr) as well as the predicted mean exposure at CCI in this study based on interpolation between the CCI mg and CCI mg exposures observed in CCI. Table 3 also compares projected exposure at the CCI mg dose level to that observed at the NOAEL in the 28-day rat

GLP toxicology study. These data indicate that the expected exposure at the CCI -mg dose level is comparable to the rat NOAEL.

Table 3. Summary of Preliminary (Unaudited) Plasma PK Parameters of Sisunatovir Following Multiple Oral Dose Administration for 5 Days in Healthy Participants in CCI, Compared to Predicted Exposures relative to Rat NOAEL

Parameter[a], Units	CCI					Rat NOAEL 60 mg/kg/day
	CCI mg Q12hr (fed), n=12[b]	CC mg Q12hr (fed), n=5	Predicted 250 mg Q12hr (fed)	Predicted 300 mg Q12hr (fed)	Predicted DDI effect on 200 mg Q12hr (fed)	
Day 5 (Steady State)						
C_{max} (ng/mL)	97.9 (65)	811.0 (41)	CCI	CCI	CCI	322
AUC_{tau} (ng.hr/mL)	787.3 (76)	7245.2 (47)	CCI	CCI	CCI	4725[c]

a geometric mean (geometric %CV).
b Data collected from 9 participants. 3 participants received CC mg (fed) in Period 1 and repeated in Period 2 after washout period.
c AUC over 24 hours.

Following evaluation of safety and sisunatovir PK data from at least 7 participants in this study, at Sponsor discretion the dose of sisunatovir may be increased to CCI provided that the projected exposure at the higher dose is no more that 20% above the rat NOAEL mean exposures for the 28 day GLP tox study. These predicted exposures would be well below the observed exposure with an acceptable safety profile from the ongoing study CCI. This will allow characterization of concentration-QTc analysis at higher exposures to more fully understand the potential effects at high clinical exposures.

Given the exposures of CCI mg Q12hr exceeded NOAEL exposures with an acceptable safety profile (Study CCI), robust monitoring of participants in the PCRU, limited duration of dosing, and variability in exposure at NOAEL of 60 mg/kg/day, crossing the mean NOAEL limits would not pose a safety concern for participants. Additionally, the toxicity findings above the NOAEL (120 mg/kg/day) were predominantly transient in nature and reversed after 14 days off treatment.

In study C5241004, coadministration with itraconazole, a strong CYP3A inhibitor, increased exposure of sisunatovir by approximately 3 to 3.5-fold. Thus, the predicted high clinical exposure for 200 mg Q12 hours under fed conditions is a C_{max} of CCI ng/mL and AUC_{tau} of CCI ng.hr/mL. The safety and PK data from approximately the first 7 participants may be assessed and if observed exposure of CCI under fed conditions is lower than predicted (see Table 3) and do not cover the high clinical exposure, then the dose will be increased to CCI, as described above. A single 400 mg dose of moxifloxacin has been used as standard positive control in QT studies and will be included as an open-label treatment.

In order to achieve therapeutic concentrations the current study will dose to steady state. Phase 1 studies indicate that steady state is achieved after approximately CCI so the current study will evaluate QTc interval at steady state on Day . Treatment A and B will receive sisunatovir and placebo CCI for doses, respectively. To maintain consistency between treatment groups, Treatment C will consist of placebo CCI for days (doses) and moxifloxacin administered on Day .

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants aged 18 to 65 years, inclusive, at the time of signing of the ICD.
   - All fertile participants must agree to use a highly effective method of contraception (See Appendix 4).
   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.
2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, including blood pressure, pulse rate, standard 12-lead ECG, and laboratory tests.

Other Inclusion Criteria:

3. BMI of 17.5 to 32 kg/m2; and a total body weight >50 kg (110 lb).

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

    - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb. Hepatitis B vaccination is allowed.

    - Positive test result for SARS-CoV-2 infection on Day -1.

2. Participants, who according to the product label for moxifloxacin, would be at increased risk if dosed with moxifloxacin, including but not limited to participants with history of myasthenia gravis, tendinitis/tendon rupture, history of hypersensitivity, allergy, severe adverse drug reaction or intolerance to quinolone antibiotics, including moxifloxacin.

3. Self-reported history or risk factors for QT prolongation or torsades de pointes (eg, organic heart disease, congestive heart failure, hypokalemia, hypomagnesaemia, congenital long QT syndrome, myocardial ischemia or infarction), congenital deafness, family history of cardiac arrest or sudden death, and family history of long QT syndrome.

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

Prior/Concomitant Therapy:

5. 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 antibiotics and 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).

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

Prior/Concurrent Clinical Study Experience:

7. 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:

8. A positive urine drug test.

9. For females, pregnancy, as indicated by a positive serum pregnancy test at screening and/or positive urine pregnancy test in WOCBP at Day -1.

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

11. 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. Participants with an average QTc interval >450 milliseconds (ms) will not be allowed to participate in the study. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - GFR <60 mL/min/1.73m2 based on CKD-EPI equation;
    - AST or ALT level ≥1.5 x ULN;
    - Gamma-GT> 1.2 x ULN;

- Alkaline phosphatase > 1.2 x ULN;
- Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusion Criteria:

13. 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).
14. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.
15. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
16. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
17. 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. 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.

- To minimize impact on baseline ECG measurement, water is restricted 1 hour prior to study intervention administration on Day 1, except with the morning meal. On Day 3, water is restricted 1 hour prior to study intervention, except with meals, and 2 hours after dosing. Participants will be restricted to consuming ambient temperature drinks from Day 1, (prior to baseline ECG measurements), until final ECG measurements have been collected in each study period. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- On dosing days, participants will consume a standard meal approximately 30 minutes prior to morning dosing. They should be encouraged to complete their meals by approximately 10 minutes prior to anticipated dosing. Lunch will be provided approximately 4 hours after dosing (ie, following the scheduled 4 hour ECG and PK measurements) and will be at approximately the same time (±15 minutes) for each study day across all dosing periods. On Day 3, standard meals should be as similar as possible for all participants.

- Dinner will be provided approximately 11 to 13 hours after AM dosing (ie, approximately 30 minutes before the PM dose) and will be at approximately the same time (±15 minutes) for each study day across all dosing periods.

- An evening snack may be permitted **after** completion of the 12-hour ECG and PK measurements.

- The timing of meals must be standardized (with an acceptable deviation of ±15 minutes) between study days and study periods. The timing of meals and snacks must be recorded. It should be noted if a participant fails to consume the majority of a meal.

- 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 and final ECG measurement 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 on Day 3, 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 8.3.5.

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 noninvestigational 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, matching placebo, and active control moxifloxacin.

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	PF-07923568 (sisunatovir)	Placebo for PF-07923568 (sisunatovir)	Moxifloxacin
Treatment Arm	A	B	C
Unit Dose Strength(s)	50 mg	Placebo	400 mg
Dose Formulation	Capsule	Capsule	Tablet
Dosage Level(s)	Planned doses are CCI* mg CCI for [redacted] doses.	0 mg CCI for [redacted] doses	400 mg moxifloxacin on Day [redacted]**
Route of Administration	Oral	Oral	Oral
Use	Experimental	Placebo-comparator	Active-comparator
IMP or NIMP/AxMP	IMP	IMP	AxMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided locally by the CRU
Packaging and Labeling	The sisunatovir 50 mg capsules will be provided in bulk. CRU Staff will prepare individual doses for administration	The placebo capsules will be provided in bulk. CRU Staff will prepare individual doses for administration	The CRU will ensure that all locally sourced moxifloxacin tablets to be used in the study are from the same lot.
SRSD	IB	IB	USPI
Current/Former Name(s) or Alias(es)	Sisunatovir PF-07923568 RV521	Placebo	Moxifloxacin Avelox, Vigamox, Moxiflox, others

* Dose will be adjusted to the highest feasible dose that is sufficient well tolerated, up to CCI .

** Sisunatovir placebo will be administered CCI for [redacted] doses, followed by a single dose of 400 mg moxifloxacin on Day [redacted].

Sisunatovir will be provided by Pfizer as 50-mg capsules at the CRU.

Matching placebo will also be provided.

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

Moxifloxacin will be supplied by the CRU.

6.1.1. Administration

Participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) approximately 30 minutes after the start of a standard breakfast that will be consumed over approximately 20 minutes. Participants will receive the evening dose of study intervention 12 hours after the morning dose (plus or minus 1 hour) approximately 30 minutes after the start of a standard dinner that will be consumed over approximately 20 minutes. In all subsequent treatment periods, the timing of dose administration for a given participant must be matched to that of the first period (±15 minutes). On Day 3 in each period only the morning dose of study intervention will be administered. Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL.Participants may receive additional ambient temperature water up to 100 mL, if needed. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling on Day 3, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

6.2. 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 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 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.

6.2.1. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.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.

PF-07923568 and placebo will be prepared by qualified unblinded site personnel. Blinded study intervention will be administered in a blinded fashion to the participant. Capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The 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's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. 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. An otherwise uninvolved third party will be responsible for administration of the drug. This includes ensuring that there are no differences in time or effort taken to administer the study intervention and no blinded site staff are able to view the administration.

6.4. Blinding

This is a double-blind (sponsor-open) study. Moxifloxacin administration on Day 3 will be unblinded.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention. Moxifloxacin administration on Day 3 will be unblinded.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention for sisunatovir and matching placebo. Moxifloxacin administration on Day 3 will be unblinded.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention for sisunatovir and placebo throughout the course of the study.

In order to maintain this blind, an otherwise uninvolved third party will be responsible for administration of sisunatovir and matching placebo. This includes ensuring that there are no differences in time or effort taken to administer the study intervention and no blinded site staff are able to view the administration.

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

PCRU Pharmacy staff responsible for preparing all study intervention will be unblinded. PCRU site staff providing technical system support to the Pharmacy staff, and supporting blinded laboratory data processes will be unblinded. These site staff providing system support are not involved in any data collection or clinic floor activities.

6.4.3. Blinding of the Sponsor

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

6.4.4. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to

unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented in a CRF.

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

6.5. Study Intervention Compliance

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

When participants are dosed 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 of sisunatovir is not allowed. The sisunatovir dose selected will be the highest feasible sufficiently tolerated dose. In this study, an initial dose of CCI has been selected to achieve high clinical exposure based on interpolation between the CCI mg and CCI mg exposures observed in CCI. The safety and PK data from approximately the first 7 participants may be assessed and if observed exposure of CCI is lower than predicted (see Table 3) and do not cover the high clinical exposure, then the dose will be increased to CCI.

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

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

6.8. Treatment of Overdose

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

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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 antibiotics and 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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- AE requiring discontinuation in investigator's view.

- Pregnancy.

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

Participants who develop a marked prolongation of the QT/QTc interval during the 3-day course with the study drug must be discontinued from further study treatment and followed for safety, especially if the measurement is obtained from more than one ECG. A marked prolongation of the QT/QTc interval is defined as a QT/QTc to >500 ms or of >60 ms over baseline.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

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

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

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

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

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

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

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

The total blood sampling volume for individual participants in this study is approximately 120 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total

volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations section 5.3 and Concomitant Therapy section 6.9 of the protocol.

8.1.1. Baseline Procedures

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

8.2. Efficacy Assessments

Not applicable

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

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

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm

(preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

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

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

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

8.3.3. Electrocardiograms

ECG measurements must be obtained prior to vital signs assessment, blood samples, and prior to dosing (note that, where scheduled at the same nominal time, the ECG measurement time must be as close as possible to the PK sampling time). It is imperative that the order and timing of all study procedures, including meal and snack times, be approximately the same (±15 minutes) across all study periods.

Standard 12-lead ECGs (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex.. 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. Environmental distractions in the clinic (TV, radio, conversation) and other study procedures (eg, BP measurement, PK sampling) during both the pre-ECG rest and the ECG recording period must be minimized. In particular, changes in heart rate should be avoided.

Triplicate 12-lead ECGs will be obtained approximately 2 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each period will serve as each participant's baseline QTcF value. 3 baseline pre-dose measurements are needed for CQT analysis, these ECGs will be done approximately 40 min, 25 min, and 10 min before the pre-dose meal. The average of the triplicate ECGs over the 3 pre-dose measurements (total of 9 ECGs) will serve as each participant's baseline QTc value.

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

repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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

Special attention should be given to ensure identical ECG lead placement during every measurement. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to an observed ECG abnormality. The lead to be used for interval measurements should be pre-specified; baseline and on-treatment measurements should be using the same lead. Every attempt should be made to use the same ECG machine throughout the study for a given participant.

In this study, a semi-automated approach to ECG acquisition will be used. This technique uses a computer algorithm for the initial placement of reference marks on the waveforms to note where on the tracing the computer is making its measurements. A standard semi-automated algorithm will be used so that a limited number of CRU staff will review program-determined interval onsets and offsets and modify using digital calipers on the rare occasion when this is necessary. Where possible, the same person should review all ECG measurements for a given participant throughout the all study periods. This review must be performed by an appropriately qualified and blinded member of CRU staff. Use of this semi-automated algorithm is designed to further improve the validity of the automated ECG readout by reducing the variability associated with interpretation of the ECG waveform. This approach can have the advantage of greater consistency and reproducibility than fully manual readings, while providing an opportunity to correct any mistakes made by the algorithmic methods. Recent evidence suggests that automated techniques are capable of detecting small changes in the QTc similar to those with manual readings and with the same conclusion.[10]

The final ECG report should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 8) and should be evaluated further, as clinically warranted.

It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

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

8.3.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

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

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

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection according to local procedures.

8.3.6. Pregnancy Testing

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

(eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention until the follow-up visit (28-35 days after last dose of study drug).
- A male participant who is receiving or has discontinued study intervention inseminates a female partner until the follow-up visit (28-35 days after last dose of study drug) for the participant.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

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

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

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

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.

Other examples include, but are not limited to:

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

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

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

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

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

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide approximately of 0.8 mL of plasma, will be collected for measurement of plasma concentrations of sisunatovir as specified in the SoA. Whole blood (approximately 2 mL) will collected at 5 and 12 hour post-dose for *in vivo* blood/plasma ratio assessment. Exploratory PK blood samples for the measurement of sisunatovir concentrations will be collected, in order to evaluate micro sampling PK approach using the Tasso® micro sampling device. Total blood volume for exploratory PK will not exceed 0.1 mL at each time point specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of sisunatovir. Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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.

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

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated 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 will be 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

9.1.1. Primary Endpoint

Concentration-QTc analysis will be used to assess if sisunatovir at maximum concentrations (C_{max}) at the CCI [redacted] has clinically relevant effect on the QTc interval at one sided $\alpha = 0.05$ level without multiplicity adjustment. After a final concentration-ΔQTc model has been established, denote the population mean of model predicted placebo-corrected ΔQTcF (ΔΔQTcF) at the C_{max} of a dose of interest as μ_{cnax}, the null hypothesis of sisunatovir having a positive QTc effect and the alternative hypothesis of sisunatovir having a negative QTc effect at the dose of interest can be expressed as the following:

H_0: $\mu_{cmax} \geq 10$ msec

H_a: $\mu_{cmax} < 10$ msec

The lack of effect of sisunatovir on QTc intervals will be concluded if the upper bound of the 2-sided 90% CI for the ΔΔQTcF estimated by the final concentration-ΔQTc model is <10 msec at the highest clinically relevant exposure.

9.1.2. Assay Sensitivity

The assay sensitivity is tested at 3, 4 and 5-hours pose-dose of positive control, moxifloxacin, on Day 3 simultaneously at one-sided $\alpha = 0.05$ level with Bonferonni correction of $\alpha/3$ for multiple assessments. Denote the population mean of change from baseline in QTcF of moxifloxacin and placebo at 3, 4, or 5-hr post-dose as μ(M) and μ(P), respectively, the statistical hypotheses are:

H_0: $\mu(M) - \mu(P) \leq 5$ msec

H_a: $\mu(M) - \mu(P) > 5$ msec

The study will be deemed adequately sensitive to detect QT/QTc prolongation if any of the lower limits of the two-sided Bonferroni-adjusted 90% CI (96.7% CI) for mean differences between moxifloxacin and placebo at any of the 3, 4 and 5-hr pose-dose, respectively, are greater than 5 msec.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study

Participant Analysis Set	Description
	following completion of the informed consent process and randomization. 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.
ECG analysis set	All participants randomized and treated who have at least 1 post-dose ECG measurement in at least 1 period. Analysis sets may contain different numbers of participants for different ECG parameters based on availability of data. Participants will be analyzed according to the product they actually received.
Concentration-QTc analysis set	The concentration QTc analysis population is defined as all participants randomized and treated with sisunatovir or placebo who have at least 1 pair of time-matched post-dose QT and sisunatovir plasma concentration values in at least 1 period of the study. For placebo treatment, the concentration of is set to 0.
PK Concentration analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value can be reported.
PK Parameter analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest can be reported.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

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.

9.3.1.1. Derivation of ECG Parameters Prior to Analyses

The average of the triplicate ECGs collected at each time point according to the SoA will be calculated and used in PK/PD modeling, statistical analyses, and/or descriptive summaries.

The QTcF is defined as Fridericia's heart rate correction, obtained using the formula:

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

The QTcB is the Bazett's heart rate correction, obtained using the formula:

- $QTcB(msec) = QT(msec)/(RR)^{1/2}$ where RR(sec) = 60/HR (if not provided)

The baseline of ECG parameters will be defined as the mean of the 3 averages of the triplicate measurements taken at the following 3 time points (approximately 40 min, 25 min, and 10 min before pre-dose meal) before dosing on Day 1 within each period. Changes from baseline ECG parameters, including changes from baseline in QTcF, uncorrected QT, QTcB , PR, QRS, and heart rate, will be calculated for each participant and treatment at each post-dose timepoint on Day 3 and 4 within each period.

The maximum absolute post-dose value and the maximum increase from baseline for QTcF, QTcB, PR, and QRS intervals will be determined for each participant and treatment. When there is no increase from baseline over the respective period, the minimum decrease will be taken.

9.3.1.2. ECG Data Summaries

Mean baseline and changes from baseline for QTcF, QTcB, QT (uncorrected), PR, QRS and heart rate will be calculated for each participant and summarized descriptively (N, mean, standard deviation [SD], median, minimum and maximum) by treatment and time postdose.

Placebo-corrected change from baseline for QTcF, QT (uncorrected) and heart rate differences will be summarized (N, mean, 90% CI) and plotted (mean) for each treatment and time point postdose.

Categorization of HR, QRS, and PR intervals will be described in the SAP. Categorization of maximum QTc will be provided for QTcF by treatment using the following criterion.

Absolute Maximum (msec)	<450	450 to <480	480 to <500	≥500
Maximum Increase from Baseline (msec)	<30	30 to <60	>60	

If any of the 3 individual ECG tracings has a QTcF value ≥500 msec, but the mean of the triplicates is < 500 msec, the data from the participant's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements

that are ≥500 msec will not be included in the categorical analyses unless the average from the triplicate measurements is also ≥500 msec.

9.3.2. Primary Endpoint Analysis

PK/PD model will be established to characterize the relationship between sisunatovir plasma concentration and change from baseline in Fridericia's heart-rate corrected QT interval (ΔQTcF) using the concentration-QTc analysis set. Based on the recommendation in the White Paper[11], the linear mixed effect model preferred is pre-specified as:

$$\Delta QTcF_{ijk} = \theta_0 + \eta_{0,i} + \theta_1 TRT_j + (\theta_2 + \eta_{1,i})C_{ijk} + \theta_3 TIME_j + \theta_4\left(QTc_{ij0} - \overline{QTc_0}\right) + \varepsilon_{ijk}$$

$\Delta QTcF_{ijk}$ is the change from baseline in QTcF for participant i in treatment j at time k; θ_0 is the population mean intercept in the absence of a treatment effect; $\eta_{0,i}$ is the random effect associated with the intercept term θ_0; θ_1 is the fixed effect associated with treatment TRT_j (0 = placebo, 1 = sisunatovir); θ_2 is the population mean slope of the assumed linear association between plasma sisunatovir concentration and $\Delta QTcF_{ijk}$; $\eta_{1,i}$ is the random effect associated with the slope θ_2; C_{ijk} is the plasma concentration of sisunatovir for participant i in treatment j and time k and $C_{ijk} = 0$ for placebo group; θ_3 is the fixed effect associated with time; and θ_4 is the fixed effect associated with centered baseline $QTcF_{ij0}$, where $\overline{QTc_0}$ is overall mean of $QTcF_{ij0}$, i.e., the mean of all the baseline (= time 0) QTcF values. It is assumed the random effects ($\eta_{0,i}$, $\eta_{1,i}$) are normally distributed with mean [0,0] and an unstructured covariance matrix, whereas the residuals ε_{ijk} are normally distributed with mean 0 and variance σ^2.

The model-derived mean ΔΔQTcF and corresponding two-sided 90% CIs will be computed at concentrations of interests eg, expected C_{max} at the [redacted]. If the upper bound of the two-sided 90% interval for the ΔΔQTcF as estimated by the final concentration-ΔQTc model established in this study is <10 msec at the highest clinically relevant exposure, the absence of an effect of sisunatovir on QTc will be concluded. The highest clinically relevant exposure (due to intrinsic and/or extrinsic factors) will be determined later from other studies.

Details of the modelling approach including the structural model, assumptions, criteria for model selection and evaluation as well as potential changes to the pre-specified model, if needed based on constraints of the available data, will be described in the SAP.

The modeling output will be reported as stand-alone report or within specific sections in the clinical study report. The information to be reported will be outlined in the SAP.

9.3.3. Secondary Endpoints Analysis

Change from baseline in QTcF intervals will be analyzed using a MMRM model with sequence, period, treatment, time (post-dose timepoint) and treatment by time interaction as fixed effects, participants as a random effect, and baseline QTcF as the covariate. A compound symmetry covariance matrix will be fitted to the repeated times within participant (other covariance matrices will be considered if necessary), and the Kenward-Roger approximation will be used for estimating degrees of freedom. The ECG analysis set will be

used for the MMRM analysis. The lower limit of the Bonferroni-adjusted 90% CI (96.7% CI) of mean difference of moxifloxacin over placebo at 3, 4, and 5-hr post-dose will be reported separately and compared to the threshold of 5 msec.

See Section 9.3.4 for the secondary endpoints of safety analyses.

9.3.4. Safety analyses

All safety analyses will be performed on the Safety Analysis Set as defined in Section 9.2.

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

Medical history and PE 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 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 by treatment:

Safety QTcF Assessment

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

9.3.5. Exploratory Endpoints Analysis

Details on the analyses of Exploratory endpoints will be described in the SAP.

9.4. Interim Analyses

No interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

A sample size of 42 (7 per sequence) participants will provide approximately 99% power to detect a 5 msec difference between moxifloxacin and placebo at historical moxifloxacin

Tmax (3 hour) to demonstrate the study sensitivity, if the expected mean difference between moxifloxacin and placebo is no less than 10 msec at Tmax.

This calculation used a 1-sided 5% paired t-test and assumed a conservative estimate of common intra-subject standard deviation of 5.61 msec for the change from baseline in QTcF, based on a previous study (C5241001). Previous PCRU TQT studies (A4301023, A3921028, A5761016, A5951151, A5271032, A4251025, A7691017 and B1811062) had an average dropout rate of approximately 2%. Assuming a 2% dropout rate, 41 participants would provide approximately 99% power to demonstrate the study sensitivity.

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. 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.

10.1.3. Data Protection

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

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

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

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

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

10.1.4. Committees Structure

10.1.4.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.5. 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.

10.1.6. 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.

10.1.7. 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.

10.1.8. 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.

10.1.9. 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 or 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.

10.1.10. 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.

10.1.11. Sponsor's Medically Qualified Individual

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

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

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. 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. 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 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine CystatinC and eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT GGT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	• Pregnancy test (β-hCG)[d] • Urine drug screening[c] • Covid-19 testing At screening: • FSH[b] • Hepatitis B surface antigen • Hepatitis B surface antibody[e] • Hepatitis B core antibody • Hepatitis C antibody • HIV

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
e. HBsAb will be tested if HBsAg and/or HBcAb is positive.

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.

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

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.

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

AE and SAE Recording/Reporting

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.

AE and SAE Recording/Reporting

- 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 10.1.8 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.

Assessment of Causality

- 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

Follow-Up of AEs and SAEs

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.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• 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 is not pregnant or breastfeeding and at least 1 of the following conditions applies:

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

  OR

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

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

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

10.4.3. Woman of Childbearing Potential

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

If fertility is unclear (eg, amenorrhea 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

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

Sexual Abstinence

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

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to sisunatovir or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
- Retained samples will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments [and Study Intervention Rechallenge Guidelines]

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, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline 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 (for adult and for pediatric participants):

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 10.7.2.1.) 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).

PEDIATRICS: Currently, no Screat plus Scys eGFR equations have been universally adopted for pediatrics. Therefore, comparison of baseline Screat and Scys to post-baseline Screat and reflex Scys are utilized to support differentiation of AKI from DIKI. Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)[12]

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

10.7.2.2. Adolescents (12 Years to <18 Years)—Cockcroft-Gault Formula

eCrCl (mL/min)

Males: eCrCl = [(140 - age) × body weight (in kg)] / [Screat (in mg/dL) × 72]

Females: eCrCl = 0.85 × [(140 - age) × body weight (in kg)] / [Screat (in mg/dL) × 72]

10.7.2.3. Children (2 Years to <12 Years)— Schwartz Equation

eCrCl normalized to BSA (mL/min/1.73 m^2)

eCrCl = (K × Ht) / Screat

Ht in cm; Screat in mg/dL.

K (proportionality constant): Female child < 12 years: K = 0.55. Male child <12 years: K = 0.70.

10.7.2.4. Infants (1 Month to <2 Years) and Neonates (<1 Month)— Schwartz Equation

eGFR (mL/min/1.73 m^2) = 0.413 × (Ht/Screat)

Ht in cm; Screat in mg/dL.

10.7.3. 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 10.7.2) 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
- Adolescents (12 years to <18 years) - Cockcroft-Gault Formula (eCrCl): https://www.kidney.org/professionals/kdoqi/gfr_calculatorCoc

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units 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.

10.7.4. 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.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • 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 seconds 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 second 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.

10.9. Appendix 9: 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 conmeds 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 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 pharmacokinetics of sisunatovir.

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

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

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

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
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			
CCI			
CCI		CCI	
CCI		CCI	
P-gp Inhibitors		**P-gp Inducers**	
Atazanavir	Lopinavir	Apalutamide	
Boceprevir	Lumacaftor	Atazanavir	
Cobicistat	Mifepristone	Fosamprenavir	
Conivaptan	Nelfinavir	Lopinavir	
Cyclosporine	ombitasvir and paritaprevir and ritonavir and dasabuvir	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	
[redacted]		
[redacted]		
Not an all-inclusive list.		

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
ADME	Absorption Distribution Metabolism Excretion
AE	adverse event
ALT	alanine aminotransferase
APD90	action potential duration at 90% repolarization
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{tau}	area under the curve from zero time to time tau, the dosing interval
AV	atrioventricular
AxMP	auxiliary medicinal product
Balb/C	albino, laboratory-bred strain of the house mouse
BBS	Biospecimen Banking System
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
Cav	Average Concentration During a Dosing Interval
CFR	Code of Federal Regulations
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	compulsory license
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CQT	Critical-To-Quality
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
CTSAE	cane toad skin aqueous extracts
CV	cardiovascular
CYP	cytochrome P450
DCT	data collection tool

Abbreviation	Term
DDI	drug-drug interaction
DIC	Deviance Information Criterion
DICI	drug-induced creatinine increase
DILI	drug-induced liver injury
DPB	Diffuse panbronchiolitis
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
ET	early termination
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
EGFR	epidermal growth factor receptor
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FIH	first in human
FSH	follicle-stimulating hormone
F/U	follow-up
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Principles of Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
hERG	the human Ether-à-go-go-Related Gene
hIPSC-CM	Human induced pluripotent stem cell derived cardiomyocytes
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document

Abbreviation	Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	Intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
Ki	Kupperman Index
LBBB	left bundle branch block
LFT	liver function test
LRTI	Lower Respiratory Tract Infections
LV	left ventricle
LVSP	Left ventricular septal pacing
MAD	Mitral annulus disjunction
CCI [redacted]	[redacted]
MMRM	mixed model for repeated measures
MQI	medically qualified individual
MTD	maximum tolerated dose
NA	not applicable
Nav	Nerve Action Potential
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
CCI [redacted]	[redacted]
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
%CV	percent coefficient of variation
P-gp	permeability glycoprotein
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PQ	Performance Qualification
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
Q	every quantity
QRS	QRS complex, represents ventricular depolarization

Abbreviation	Term
QT	QT interval is the time from the start of the Q wave to the end of the T wave
QTc	corrected QT interval
QTcB	QT corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
QTcV	QT conduction velocity
qual	qualitative
Q&As	questions and answers
RBC	red blood cell
RR	Respiration rate
RSV	Respiratory Syncytial Virus
RSV-F	The respiratory syncytial virus F glycoprotein
SAD	Seasonal affective disorder
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scys	serum cystatin C
SoA	schedule of activities
SOC	Specialist Outpatient Clinic
SOP	standard operating procedure
SRSD	Single Reference Safety Document
ST-T	ST-segment and T-wave
SUSAR	Suspected Unexpected Serious Adverse Reaction
T bili	total bilirubin
TdP	Torsades de pointes
TEAE	Treatment emergent adverse events
THC	tetrahydrocannabinol
TI	therapeutic index
Tmax	Time to peak drug concentration
TQT	Total Quality Transformation
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
WBC	white blood cell
WOCBP	woman/women of childbearing potential
ycAPD90	yc AP durations at 90% repolarization

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