Title Page

AN INTERVENTIONAL PHASE 2/3, ADAPTIVE, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO INVESTIGATE EFFICACY AND SAFETY OF ORAL SISUNATOVIR COMPARED WITH PLACEBO IN NON-HOSPITALIZED SYMPTOMATIC ADULTS WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION WHO ARE AT RISK OF PROGRESSION TO SEVERE ILLNESS

Study Intervention Number:	PF-07923568
Study Intervention Name:	Sisunatovir
US IND Number:	143479
EU CT Number:	2023-505922-32-01
ClinicalTrials.gov ID:	NCT06079320
Pediatric Investigational Plan Number:	EMEA-002529-PIP02-23
Protocol Number:	C5241007
Phase:	Phase 2/3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Determine if the Study Medicine Called Sisunatovir is Safe and Prevents Severe Illness in Adults with Respiratory Syncytial Virus Infection

Document History

Document	Version Date
Protocol Amendment 1	30 April 2024
Original protocol	1 September 2023

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

Protocol Amendment Summary of Changes Table

Amendment 1.0 30 April 2024

Overall Rationale for the Amendment: The main modifications in this Protocol Amendment are to expand the primary analysis population in response to external regulatory feedback as well as to add a PK interim analysis, add optional PK sampling, and to update the ECG requirements based on new safety data.

Description of Change.	Brief Rationale	Section # and Name
Substantial Modification(s)		
The primary estimand was expanded to include all randomized participants who received a dose of study drug, regardless of days since symptom onset. The first key secondary endpoint was removed accordingly. These changes are incorporated into the study objectives, endpoints, estimands, overall design, analysis set definitions, and statistical methods, as required.	These updates were made in response to external regulatory feedback to allow the study population to be as inclusive as possible of the broader study population in regards to symptom duration, and to have more participants contribute to the primary objective.	Protocol Summary Section 3 Objectives, Endpoints and Estimands Section 4.1 Overall Design Section 9.1.1.1 Primary Estimand Section 9.1.1.2 Secondary Estimand Section 9.1.2 Multiplicity Adjustment Section 9.2 Analysis Sets Section 9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis Section 9.5 Sample Size Determination
The primary analysis methodology for the primary estimand and several key secondary endpoints was changed.	This update was made in response to external regulatory feedback regarding handling of participants who discontinue from the study early. The updated methodology provides for imputation of responses for these participants.	Section 9.3.2.2 Main Analytical Approach Section 9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis
The required efficacy to continue at the futility interim analyses was	The gamma parameter for the beta spending function was increased	Protocol Summary

Description of Change.	Brief Rationale	Section # and Name
increased and the sample size requirements for the study were adjusted.	from 0 to 1 to increase confidence in future results. The required total sample size for the study was recalculated accordingly, also allowing for loss of participants from the primary analysis set due to negative PCR results.	Section 4.1 Overall Design Section 4.2.5 Rationale for Adaptive or Novel Study Design Section 9.3.2.2 Main Analytical Approach Section 9.4 Interim Analyses Section 9.5 Sample Size Determination
The timing of efficacy interim analyses 1 and 2 were modified and an additional interim analysis was added for a PK evaluation.	The timing of efficacy interim analysis 1 was moved from 35% enrollment to 45% enrollment to improve the performance of the futility assessment. The timing of efficacy interim analysis 2 was moved from 60% to 65% to improve the performance of efficacy assessments. A PK interim analysis was added to evaluate steady-state exposures.	Protocol Summary Section 4.1 Overall Design Section 6.4.3 Blinding of the Sponsor Section 9.4 Interim Analyses Section 9.5 Sample Size Determination
ECG removed from Visits 3 and 5, and baseline ECG changed to a single collection.	The CCI [redacted] demonstrated that sisunatovir did not have a clinically relevant effect on QT interval.	Table 1 Schedule of Activities Section 2.2.4 Clinical Overview Section 2.4.1 Risk Assessment Section 7.1.3 ECG Changes Section 8.3.3 Electrocardiograms Section 9.3.5 Safety Analyses (Electrocardiogram Analyses)
Inclusion criterion #2 updated to indicate that diagnosis of RSV may be determined by a locally available RSV test.	The criterion was modified to be more inclusive of site testing capacity.	Protocol Summary Section 5.1 Inclusion Criteria
Exclusion criteria #4 and #5 updated to remove/revise medical or medication restrictions due to QT_C prolongation.	The criteria were modified in consideration of the results of the CCI [redacted] which showed no evidence of prolongation of QTc interval.	Protocol Summary Section 2.4.1 Risk Assessment Section 5.2 Exclusion Criteria Section 6.9 Prior and Concomitant Therapy Section 10.9 Appendix 9: Prohibited Concomitant Medications
Addition of optional additional PK collection in approximately CCI participants CCI [redacted]	PK blood collection using the Tasso® M20 microsampling was removed from the protocol due to incompatibility with sisunatovir. Therefore, a subset of participants will be included in a PK substudy	Protocol Summary Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 8.5 Pharmacokinetics

Description of Change.	Brief Rationale	Section # and Name
	to collect post-dose samples to inform population PK modeling.	
Clarified restrictions on prohibited prior and concomitant medications, including the creation of new sections on Sensitive NTI CYP3A4 Substrates and Acid Reducing Agents.	The updates are to clarify the medication restrictions and exclude the use of PPI and H2 blockers based on preliminary clinical pharmacology data.	Section 6.9. Prior and Concomitant Therapy Section 10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI
The minimum total blood sampling volume for individual participants is reduced from 80 mL to 70 mL, and 90 mL for participants in the optional PK sampling collection. An additional clarification is made to the amount of blood required for Specified Protein Research.	Total blood sampling volume updated based on changes in PK collection schedule.	Section 8.1 Administrative and Baseline Procedures Section 8.7.3 Specified Protein Research
Updates were made to the sections on biomarkers and biological specimens to clarify what tests will be performed and when.	Additional language was added to clarify the allowed specimen types and what the specimens will be used for.	Table 1 Schedule of Activities Section 8.1.1 Baseline Procedures Section 8.7 Biomarkers Section 8.7.1 Pharmacodynamic Biomarkers
Non-substantial Modification(s)		
In the SoA, a note is added to the rows on retained research specimens that these specimens are only required at an early discontinuation visit if that visit occurs on or before Day 15.	This update clarifies when these samples should be collected.	Table 1 Schedule of Activities
The Table on Criteria for ARI was moved into the section on Clinical Response, and clarifications on the definitions of the Clinical Response were made.	This change helps to clarify the criteria to be followed when conducting the Clinical Response assessment.	Section 8.2.3 Clinical Response
Informed consent for the Optional Long-Term Follow up may be obtained at any visit up to Day 28. Instructions on how to generate a token for the additional research were modified in the Appendix.	Data transfer does not occur until Day 28, and therefore it is acceptable to consent or decline to participate in the Long-Term Follow up at any time up until then. The update to the site instructions in Appendix 10 will help to clarify the process.	Table 1 Schedule of Activities Section 10.10.1 United States

Description of Change.	Brief Rationale	Section # and Name
New clinical and non-clinical data added and/or updated, including the number and list of studies and patients exposed to sisunatovir.	Incorporated most current clinical and pre-clinical data into the protocol.	Section 2.2.2 Nonclinical Pharmacokinetics and Metabolism Section 2.2.4 Clinical Overview
Additional dose justification language added based on QSP viral dynamics modeling.	The developed QSP viral dynamics model supports the dose regimen of CCI mg CCI for 5 days (CCI doses).	4.3. Justification for Dose
A statement on donation and cryopreservation of germ cells was removed.	The classification category on the risks of sisunatovir supports this update on fertility risks based on available genotoxicity data, which provides the rationale for the contraception category.	Section 5.3.1 Contraception
Clarifications made that the onset of signs and/or symptoms and the diagnosis of RSV must be within 5 days of randomization	This clarification is made to ensure that randomization occurs no later than the 5th day, where the day of onset of signs and/or symptoms or RSV diagnosis is the 1st day.	Protocol Summary 4.1 Overall design 5.1 Inclusion criteria 5.4 Pre-screening consent and pre-screening viral testing (optional, if applicable)
CCI [redacted]	[redacted]	Section 6.3 Assignment to Study Intervention
Removed language that is redundant or not relevant related to safety reporting.	This change was made to align with the current protocol template	Section 8.4.1.2 Recording Nonserious AEs and SAEs on the CRF
Clarifications and updates to the planned statistical methodology are made.	Updates are generally intended to address external regulatory feedback regarding clarification or addition of analyses.	Section 9.1.1.1 Primary Estimand Section 9.1.1.2 Secondary Estimands Section 9.1.2 Multiplicity Adjustment Section 9.3.2.2 Main Analytical Approach Section 9.3.2.3 Sensitivity Analyses Section 9.3.2.4 Supplementary Analyses Section 9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis 9.3.3.1 Pharmacokinetics 9.3.5 Safety Analyses Section 9.4 Interim Analyses Section 9.5 Sample Size Determination
Country Specific section on France removed from appendices	France is not a participating country	Section 10.10.2 France

Description of Change.	**Brief Rationale**	**Section # and Name**
The entries for the EU CT number and the ClinicalTrials.gov ID were modified	The EU CT number will change during resubmission from 2023-505922-32-00 to 2023-505922-32-01. The ClinicalTrials.gov ID number was added.	Title page Section 1.1 Synopsis
Other editorial changes as required.	To correct grammatical errors, to maintain consistency, and/or to increase clarity.	Throughout the protocol
The primary method of PK sample collection in the original protocol is self-collection using the Tasso® M20 microsampling device for measurement of whole blood concentrations of sisunatovir. This amendment will remove the Tasso® M20 microsampling method from this study, and therefore all sites will default to alternate collection methods, as outlined in the protocol. Due to the removal of Tasso micro sampling, the Sponsor recommends collection of a venous PK sparse sample, preferably during the planned Day 3 and Day 5 visits.	The proposed timing of the venous PK sparse samples will support determining the PK of sisunatovir in non-hospitalized adults at high risk for severe illness. The rationale for this change is the suspected instability of sisunatovir while in liquid whole blood state during the process of drying the collected Tasso microsamples (based on assay method development and validation activities). This update is reflected in a Protocol Administrative Change Letter dated 25 September 2023.	Table 1 Schedule of Activities Section 8.1.1; Baseline Procedures Section 8.5; Pharmacokinetics Section 8.5.1, Tasso M20 Training Samples
Clarification that for participants who provide pre-screening informed consent, the active collection period ends 30 minutes after collection of the pre-screening viral testing or once viral testing results become available, whichever occurs first.	The time period for collecting and reporting AE and SAE information for participants in the pre-screening phase will end at the same time regardless of whether they ultimately enroll in the main study. For participants who enroll into the main study, the time period for AE/SAE reporting will begin again once a main study informed consent is signed. This update was reflected in a Protocol Administrative Change Letter dated 25 September 2023	Section 8.4.1, Time Period and Frequency for Collecting AE and SAE Information
CCI [redacted]	CCI [redacted]	Section 2.2.4 Clinical Overview Section 6.1.1. Administration

Description of Change.	Brief Rationale	Section # and Name
CCI [redacted]	CCI [redacted] This update is reflected in a Protocol Administrative Change Letter dated 06 November 2023.	
Text was added to clarify that retained research samples will not be collected in participants consented in China. A statement was also added to describe the process for destruction of biological samples in China.	This change was made per local regulatory requirements. This update was communicated in a country-specific Protocol Administrative Change Letter dated 14 November 2023.	Section 8.6.2 Retained Research Samples for Genetics Section 8.7.5 Retained Research Samples for Biomarkers Section 10.10.2 China
Country Specific section on the United Kingdom added as 10.10.3 to clarify country-specific requirements	WOCBP enrolled in the United Kingdom will undergo a serum or whole blood pregnancy test at the screening visit to confirm negative pregnancy prior to first dose. This was included as part of a Protocol Administrative Change Letter dated 05 February 2024	Section 10.10.3 United Kingdom
The Emergency Contact Card is being replaced by a study information card	To facilitate direct contact between site and sponsor medically qualified individual using a Study Team Contact List and for participants to show study information to other health care providers using the card. This update is reflected in a Protocol Administrative Change Letter dated 13 February 2024.	Section 10.1.12 Sponsor's Medically Qualified Individual Appendix 11: Abbreviations

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Interventional Phase 2/3, Adaptive, Multi-Center, Randomized, Double-Blind Study To Investigate Efficacy And Safety Of Oral Sisunatovir Compared With Placebo In Non-Hospitalized Symptomatic Adults With Respiratory Syncytial Virus Infection Who Are At Risk Of Progression To Severe Illness

Brief Title:

A Study to Determine if the Study Medicine Called Sisunatovir is Safe and Prevents Severe Illness in Adults with Respiratory Syncytial Virus Infection

Regulatory Agency Identification Number(s):

US IND Number:	143479
EU CT Number:	2023-505922-32-01
ClinicalTrials.gov ID:	NCT06079320
Pediatric Investigational Plan Number:	EMEA-002529-PIP02-23
Protocol Number:	C5241007
Phase:	Phase 2/3

Rationale:

Older adults and individuals affected by cardiopulmonary comorbidities or compromised immune system are at increased risk of poor clinical outcomes following respiratory syncytial virus (RSV) infection. Currently, no oral treatment is approved for this indication. The purpose of this trial is to investigate the safety and efficacy of orally administered sisunatovir, a potent inhibitor of the RSV F protein that prevents entry into the host cells, for the treatment of RSV infection in non-hospitalized adults at risk of severe illness.

Objectives, Endpoints, and Estimands:

All objectives, endpoints, and estimands will be evaluated in non-hospitalized adults who are infected with RSV and are at high risk of severe illness. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications. The primary analysis and key secondary analyses are conducted in adults with confirmed RSV infection.

Objectives	Endpoints	Estimands
Primary:		
• To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with RSV-related hospitalization or death from any cause through Day 28.	• The difference in treatment proportions of patients experiencing RSV-related hospitalization or death from any cause through Day 28.
Key Secondary:		
• To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with RSV-related visits (urgent care/emergency department [ED]/hospital) or death from any cause through Day 28.	• The difference in treatment proportions of patients experiencing RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28. A hospital visit of any duration will be included.
	• Proportion of participants with progression of lower respiratory tract infection (LRTI) through Day 10.	• The difference in treatment proportions of patients with progression of LRTI through Day 10 will be evaluated in the population of participants who do not have RSV-related severe LRTI (sLRTI-RSV) at randomization.
	• Proportion of participants with development of LRTI through Day 10.	• The difference in treatment proportions of patients who develop sLRTI-RSV or RSV-related non-severe LRTI (nsLRTI-RSV) through Day 10 will be evaluated in the population of participants who do not have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Proportion of participants with resolution of LRTI at Day 15.	• The difference in treatment proportions of patients with resolution of LRTI at Day 15 will be evaluated in the population of participants who have sLRTI-RSV nsLRTI-RSV at randomization.
	• Mean number of days alive and free from hospital stay (hospital-free days) through Day 28.	• The difference in treatment means of number of days alive and free from hospital stay (hospital-free days) through Day 28.
Other Secondary:		
• To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with progression of LRTI through Day 3, 5, 15, and 28.	• The difference in treatment proportions of patients with progression of LRTI through Day 3, 5, 15, and 28 will be evaluated in the population of participants who do not have sLRTI-RSV at randomization.
	• Proportion of participants with development of LRTI through Day 3, 5, 15, and 28.	• The difference in treatment proportions of patients who develop sLRTI-RSV or nsLRTI-RSV through Day 3, 5, 15, and 28 will be evaluated in the population of participants who do not have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Proportion of participants with resolution of LRTI at Day 3, 5, 10, and 28.	• The difference in treatment proportions of patients with resolution of LRTI at Day 3, 5, 10, and 28 will be evaluated in the population of participants who have sLRTI-RSV or nsLRTI-RSV at randomization.

Objectives	Endpoints	Estimands
	• Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28.	• The difference in treatment proportions of patients with improvement in LRTI status at Day 3, 5, 10, 15, and 28 will be evaluated in the population of participants who have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Number of RSV related days in hospital through Day 28. • Number of RSV related days in the intensive care unit (ICU) through Day 28.	• The difference in treatment means of number of RSV related days in hospital and separately, number of RSV related days in ICU, through Day 28.
	• Proportion of participants with a clinical response of Improvement or Resolution at Day 5, 10, 15, and 28.	• The difference in treatment proportions of patients with Improvement or Resolution at Day 5, 10, 15, and 28.
• To compare nasopharyngeal (NP) viral load changes among non-hospitalized adults at high risk for severe illness treated with sisunatovir relative to placebo.	• Proportion of participants with undetectable RSV viral load at each study visit through Day 28. • Change from baseline in RSV viral load at each study visit through Day 28.	• The difference in treatment proportions of patients with undetectable RSV viral load at each visit through Day 28 • The difference in treatment means of change from baseline in RSV viral load at each study visit through Day 28.
• To describe the safety and tolerability of sisunatovir relative to placebo among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with treatment emergent adverse events (TEAEs) through Day 35 • Proportion of participants with SAEs through Day 35.	• NA.
• To determine the pharmacokinetic (PK) of sisunatovir among non-hospitalized adults at high risk for severe illness.	• Plasma concentrations of sisunatovir at steady state (Day 3 or later).	• NA.

Overall Design:

This is an interventional efficacy and safety phase 2/3, superiority, multi-center, randomized, double-blind, placebo-controlled, adaptive study. Approximately 2375 symptomatic adult participants with RSV infection who are at increased risk of progression to severe illness will be randomized 1:1 to receive either oral sisunatovir CCI mg every CCI for 5 days (CCI doses), or matching placebo. Randomization will be CCI at baseline.

- Enrollment of participants with CCI randomization will be limited to approximately CCI%.
- Enrollment of participants CCI with none of the other risk factors that are listed as inclusion criteria will be limited to approximately CCI%.

Interim analyses:

- Efficacy interim analysis (IA) 1: a planned interim analysis for futility will be done after approximately 45% of participants in the primary analysis set complete Day 28 assessments or have discontinued the study.
- Efficacy IA 2: a planned interim analysis for early efficacy and futility with a sample size re-estimation will be done after approximately 65% of participants in the primary analysis set complete Day 28 assessments or have discontinued the study.
- PK IA: a planned PK IA to evaluate steady-state exposures, including trough (pre-dose) concentration at steady state ($C_{troughSS}$), will be done after at CCI participants randomized (approximately C CCI participants in the PK concentration population) have completed the CCI PK assessments.

The total study duration for each participant is up to 5 weeks and includes a screening period of 1-2 days where Day 1 of study intervention must start by the second consecutive day, study intervention administration through Day 5, efficacy outcome assessments through Day 28, and a safety follow-up period through Day 35.

An external data monitoring committee (E-DMC) will review blinded and unblinded data to ensure the safety of participants on an ongoing basis throughout the entire duration of the study. The E-DMC will also review data from each of the two planned efficacy IAs, as specified in the E-DMC Charter. When the PK IA is performed, an internal, independent, unblinded review committee separate from the study team will review population PK model-derived plasma concentration-time curves and PK parameters for sisunatovir. No safety or efficacy data will be used to inform the PK IA.

Participants in the United States will be invited to participate in optional, additional research using real world data to describe long-term health outcomes and healthcare utilization.

Number of Participants:

Approximately 2375 participants will be enrolled in the study. Sample size calculations determined that[CCI] randomized participants are required for the primary analysis. Assuming a[CCI], the required total sample size for the primary analysis will be increased to approximately[CCI] participants. Assumin[CCI] and thus will not be included in the primary analysis, the planned total number of participants to be randomized will be increased to approximately 2375. However, study enrollment will be stopped after approximately[CCI] participants are available for the primary analysis. Sample size re-assessment at the time of the second efficacy IA allows for an[CCI] with a maximum sample size of approximately[CCI]

Approximately[CCI] participants[CCI] will be invited to participate in an optional, additional PK sampling collection to provide robust steady-state PK in RSV patients to inform the population PK model.

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

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Participants aged 18 years or older (or the minimum age of consent, if above 18, in accordance with local regulations) at screening.

   - Women of childbearing potential must agree to use highly effective contraception.

2. Diagnosis of RSV infection, as determined by a RT-PCR, rapid antigen test, or other locally available diagnostic test in any respiratory specimen (eg, nasal, nasopharyngeal swab, sputum) collected within 5 days of randomization. Randomization must occur no later than the 5th day since the diagnosis of RSV infection where the day of RSV diagnosis is the 1st day.

3. New onset or worsening (if present chronically) of at least one of the following signs and/or symptoms consistent with a viral acute respiratory infection (ARI), within 5 days prior to randomization: nasal congestion, nasal discharge, sore throat, cough, sputum production, shortness of breath, or wheezing. Randomization must occur no later than the 5th day, where the day of onset/worsening is the 1st day.

4. Has at least 1 of the following characteristics or underlying medical conditions:

    - 65 years of age or older.

    - Chronic lung disease that is symptomatic or requiring treatment, including but not limited to: chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), pulmonary fibrosis (PF), pulmonary arterial hypertension (PAH), alpha-1 anti-trypsin deficiency, or pulmonary sarcoidosis.

    - Heart failure (functional class II-IV according to New York Heart Association [NYHA] classification).

    - Immunosuppressive disease or condition (eg, hematological malignancy, chimeric antigen receptor T-cell [CAR-T], bone marrow or organ transplant recipient, primary immune deficiency, or human immunodeficiency virus [HIV] infection with cluster of differentiation (CD) 4^+ cell count <200 / μL within the last 6 months) OR use of at least 1 of the following immune-weakening medications:

        - Recent treatment with corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days, all of which must have been within the last 30 days prior to study entry OR are currently receiving ≥20 mg daily that must have been administered for at least 14 consecutive days at the time of study entry.

        - Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumor necrosis factor (TNF) blockers, or other highly immunosuppressive drugs such as biologics (eg, ustekinumab, anti-CD20).

Exclusion Criteria

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

1. Any medical condition (eg, confirmed concurrent active systemic infection other than RSV including bacterial, fungal, or viral) or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study or interfere with the evaluation of response to the study intervention.

2. Diagnosis of viral respiratory infections other than RSV including influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), within 7 days of randomization. A negative test for SARS-CoV-2 and influenza is required within 7 days of randomization.

3. Current need for hospitalization or anticipated need for hospitalization for any reason to provide inpatient/acute care within 24 hours after randomization in the clinical opinion of the site investigator.

4. Any clinically significant ECG abnormality in the pre-dose ECG that, per investigator judgement, may affect participant safety.

5. Current or recent use of any prohibited concomitant medication that may result in a clinically significant drug-drug interaction.

6. Use of oral or inhaled ribavirin in prior 30 days or anticipated use during the study.

7. Prior administration of study drug in a sisunatovir trial, recent administration of an investigational drug or vaccine (within 30 days or 5 half-lives), or concurrent participation in a study of another investigational drug or vaccine.

8. Renal impairment defined by an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or receiving dialysis.

9. Active liver disease with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 upper limit of normal (ULN), or Total bilirubin ≥2 × ULN (For Gilbert's syndrome, direct bilirubin >ULN is exclusionary) within the past 3 months, or liver function impairment with Class B or C per Child Pugh classification.

10. Has hypersensitivity to or other contraindication to any of the components of the study interventions, as determined by the investigator.

11. 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:

Total duration of study participation for each participant is approximatively 5 weeks (Day 35 ± 2 days) divided as follows:

- Screening and Randomization procedures can be on the same day or over two consecutive days. The participant must be randomized by the second day (Day 1 of study intervention).

- A 5-day dosing period; If the first dose of study intervention is administered at a time that would only allow one dose to be taken on Day 1, the dosing period will continue until Day 6 to allow for a total of [redacted] doses.

- A 4-week follow-up period after the last study intervention dose.

Study Intervention(s)		
Intervention Name	Sisunatovir [redacted]mg	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	Investigational medicinal product (IMP)	IMP
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	100 mg	0 mg
Route of Administration	Oral	Oral
Study Arm(s)		
Arm Title	Sisunatovir	Placebo
Arm Description	Participants will receive [redacted] tablets of 100 mg of sisunatovir [redacted] from Day 1 to Day 5 ([redacted] doses).	Participants will receive [redacted] matching placebo tablets [redacted] from Day 1 to Day 5 ([redacted] doses).

Statistical Methods:

The primary estimand is the difference in treatment proportions of participants experiencing RSV-related hospitalization or death from any cause through Day 28 in non-hospitalized adults with RSV infection who are at increased risk of progression to severe illness. This will be estimated irrespective of compliance to the planned course of treatment or use of concomitant medications.

The primary analysis will also be conducted for the two planned efficacy IAs. Two-sided 95% CI (adjusted for the planned IAs) and associated p-value for the null hypothesis of no difference between treatment groups will be presented. Significance level for the primary assessment of efficacy will be determined using the [redacted] h at the second efficacy IA and the final analysis. Significance level for assessment of futility will be determined using th [redacted] approach at the first and second efficacy IAs. The overall significance level is set at 2.5% (1 sided).

This study is designed to have 90% statistical power to show a difference between the treatment arms (sisunatovir versus placebo) of [redacted]% in the proportion of participants hospitalized/dying, using a 1-sided Type I error rate of 2.5%. The proportion of hospitalization/death in the placebo arm is assumed to be [redacted]%. A [redacted]% absolute difference represents a [redacted]% relative reduction from placebo.

For a 2-sample proportion test, the sample size needed to detect this difference with 90% power at a 1-sided significance level of 2.5% was determined to be [redacted] randomized participants. Assuming a [redacted], the required total sample size for the primary analysis will be increased to approximately [redacted] participants. Assuming [redacted]

CCI [redacted] as measured by the central laboratory, and thus will not be included in the primary analysis, the planned total number of participants to be randomized will be increased to approximately 2375. However, study enrollment will be stopped after approximately CCI participants are available for the primary analysis.

Enrollment of participants with CCI [redacted] will be limited to approximately CCI %. Participants CCI with none of the other risk factors will be limited to approximately CCI % of the randomized participants.

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of RSV-related hospitalization or death in the primary analysis population, and about the treatment effect of sisunatovir. Hence, a sample size re-assessment will be conducted during the second efficacy IA based on conditional power. The sample size can be adjusted one time and the increase will be capped at CCI A well-established method described by Cui, Hung, and Wang will be used to control the Type I error probability.

The nominal significance level for the planned interim and final proportion of hospitalization/death primary analyses is determined by means of the CCI [redacted], with an overall 1-sided type I error rate of 2.5%.

To control familywise type I error, key secondary endpoints will be tested in a hierarchical manner.

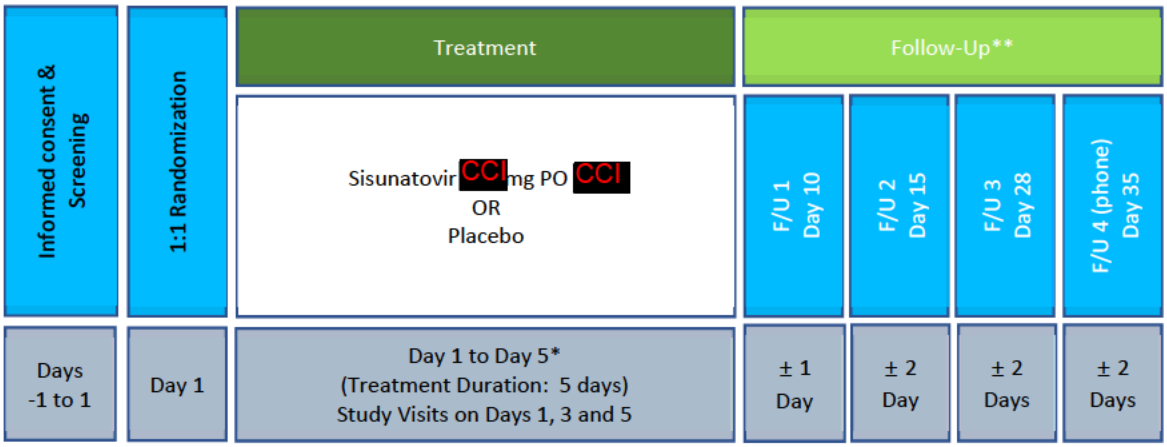
Approximately CCI participants CCI [redacted] will have additional PK sampling timepoints to collect steady-state PK in RSV patients to inform the population PK model.

Ethical Considerations:

This is a placebo-controlled trial that will be conducted in non-hospitalized symptomatic adults with RSV infection who are at increased risk of progression to severe illness. In previous studies, sisunatovir has shown to significantly reduce the nasal viral load in healthy volunteers infected with RSV in a challenge model, with consequent shortening of RSV related symptoms duration, compared to placebo. Participants enrolled may (or may not) benefit from the treatment with an antiviral. Current management of RSV infection is primarily supportive; thus, a placebo-controlled trial is justifiable for development of an RSV antiviral. There is no approved antiviral for the treatment of RSV in adults. At any time during the trial, participants will be able to access standard of care treatments, as per local medical practice.

The trial-specific risks and burdens for participants also include potential adverse events of the study medicine (sisunatovir), the requirement for multiple visits, and discomforts while undergoing study assessments (eg, blood draws, ECGs, nasopharyngeal swabs).

1.2. Schema



*Treatment duration to extend into Day 6 if the first dose is taken in the evening of Day 1.

** An unplanned visit for post-treatment ARI can be conducted between Day 6 to Day 28.

1.3. Schedule of Activities

The schedule of activities (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 (Table 1), in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	**Pre-screen** (Optional)	**Screen**	**Treatment Period**			**F/U**					**Early Discont.**	**Notes**
			Day 1	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 28**	**Day 35**	**Unplanned Visit for Post-Treatment ARI (in-person)**		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Pre-screening informed consent and pre-screening viral testing (optional, if applicable)	X											• See Section 5.4.
Informed consent		X										• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Informed consent for long-term follow-up (US only)			X									• Participation is optional. The long-term follow-up study should be discussed on Day 1, and informed consent may be obtained any time between Day 1 and Day 28 • See Section 10.10.1.
Screen for inclusion/exclusion criteria		X	X									• See Section 5.1 and Section 5.2. • Screening period can begin one day before first dose or can be the same day as the first dose.

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	**Pre-screen** (Optional)	**Screen**	**Treatment Period**			**F/U**					**Early Discont.**	**Notes**
			Day 1	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 28**	**Day 35**	**Unplanned Visit for Post-Treatment ARI (in-person)**		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Demographics		X										• See Section 8.1.1.
Randomization			X									• It is preferable for screening and randomization to occur on the same day. • If screening occurs over 2 consecutive days, randomization must occur on the second day. • Randomization and treatment start on the same day. • At randomization, the participant enrolment number is assigned.
Medical History and Physical Examination												
Medical History		X										
Physical examination		X	X								X	• Physical examination at days 3, 5, 10, 15, 28, 35, and the unplanned visit to be performed at discretion of the investigator. • Physical examinations to be completed before administration of study intervention. • A general physical examination is to be performed at screening/baseline on all participants, thereafter symptoms' driven. • If screening and randomization happen on the same day, examination performed only once. • See Section 8.3.1 for additional information.

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	Pre-screen (Optional)	Screen	Treatment Period			F/U					Early Discont.	Notes
			Day 1	Day 3	Day 5	Day 10	Day 15	Day 28	Day 35	Unplanned Visit for Post-Treatment ARI (in-person)		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Record signs and symptoms to confirm LRTI status		X	X	X	X	X	X	X		X	X	• If screening and randomization happen on the same day, LRTI status is assessed only once on Day 1.
Assess clinical response					X	X	X	X				• See Section 8.2.3.
Weight, height		X										• See Section 8.3.1 for additional information.
Vital signs		X	X	X	X	X	X	X		X	X	• If screening and randomization happen on the same day, vital signs are collected only once. • Vital signs at day 35 visit to be performed at discretion of the investigator. • See Section 8.3.2 for additional information.
12-Lead ECG		X										• ECG to be performed after screening only as needed per investigator discretion. • See Section 8.3.3 for additional information.
Contraception check		X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments												• See Section 8.3.4 for additional information. • See Section 10.2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
Hematology			X		X							• Hematology bloods at days 3, 10, 15, 28, 35, unplanned and early discontinuation visit to be performed at discretion of the investigator. • Day 1 hematology sample taken before first dose of study intervention.

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	Pre-screen (Optional)	Screen	Treatment Period			F/U					Early Discont.	Notes
			Day 1	Day 3	Day 5	Day 10	Day 15	Day 28	Day 35	Unplanned Visit for Post-Treatment ARI (in-person)		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
												• Required at Early Discontinuation visit if this visit is during the treatment period.
Blood chemistry			X		X							• Blood chemistry at Days 3, 10, 15, 28, 35, unplanned and early discontinuation visit to be performed at discretion of the investigator. • Day 1 blood chemistry sample taken before first dose of study intervention. • Required at Early Discontinuation visit if this visit is during the treatment period.
Viral testing for study eligibility		X										• Rapid viral testing at screening performed if participant does not provide negative SARS-CoV-2 and influenza tests within 7 days of randomization. • See Section 8.1.1.
Pregnancy test		X						X			X	• To be performed only for female participants of childbearing potential. • Performed at any time in case of missed menstrual cycle or suspected pregnancy throughout the study. • See Section 10.4.4 and 8.3.5 for additional information.
FSH (see notes)		X										• FSH is to be performed to confirm postmenopausal status in female participants <60 years of age at screening who are not using

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	Pre-screen (Optional)	Screen	Treatment Period			F/U					Early Discont.	Notes
			Day 1	Day 3	Day 5	Day 10	Day 15	Day 28	Day 35	Unplanned Visit for Post-Treatment ARI (in-person)		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
												hormonal contraception or hormonal replacement therapy. • When FSH testing is required to confirm postmenopausal status, a participant may be enrolled in the study prior to the test result being available if the FSH test result confirms postmenopausal status prior to dosing. A female whose menopausal status is in doubt will be required to use a highly effective method of contraception during the study. • See Section 10.4 for additional information.
PK Assessments												
PK sampling				X	X							• On Day 3, one blood sample for PK will be collected between 3 and 8 hours CCI [redacted]. On Day 5, one pre-dose blood sample for PK will be collected. The preferred time of sample collection is pre-dose up to 2 hours before study intervention; if a pre-dose sample collection is not possible, collect this sample at any time during the visit, even after the study intervention has been administered. • Approximately CCI [redacted] participants will have 8 blood samples for PK collected on Day 5 at pre-dose, 1.5, 3, 4, 5, 6, 8, and 10 hours post-dose.
Biomarker Assessments												

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	**Pre-screen** (Optional)	**Screen**	**Treatment Period**			**F/U**					**Early Discont.**	**Notes**
			Day 1	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 28**	**Day 35**	**Unplanned Visit for Post-Treatment ARI (in-person)**		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
NP swab			X	X	X	X	X	X		X	X	• Day 1 NP swab sample is collected pre-dose. • See Section 8.7
Plasma collection for specific biomarkers			X		X		X				X	• See Section 8.7.3.
Retained research sample for genetics (Prep D1)			X		X		X				X	• If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.6.2 • Only required at an Early Discontinuation if the visit occurs prior to or at Day 15.
Retained research samples for biomarkers (Prep R1, Prep B2.5)			X		X		X				X	• See Section 8.7.5. • Only required at an Early Discontinuation if the visit occurs prior to or at Day 15
Study Intervention and Other Treatments												• See Section 6 for additional information.
Dispense study intervention			X									• Study intervention is dispensed on the day of randomization (Day 1). • See Section 6.1 for additional information.
Study intervention administration			Day 1 through Day 5 (CCI doses total)									• If 1 dose was administered on Day 1, study intervention will end on Day 6 (total of CCI doses). Subsequent doses after the Day 5 visit can be self-administered outside the study clinic (eg, home). • See Section 6.1 for additional information.

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	**Pre-screen** (Optional)	**Screen**	**Treatment Period**			**F/U**					**Early Discont.**	**Notes**
			Day 1	**Day 3**	**Day 5**	**Day 10**	**Day 15**	**Day 28**	**Day 35**	**Unplanned Visit for Post-Treatment ARI (in-person)**		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Participant completes dosing log			Day 1 through Day 5 (CCI doses total)									• See Section 6.5. • If 1 dose was administered on Day 1, study intervention will end on Day 6 (total of CCI doses).
Study intervention accountability and review of dosing log			X	X	X	X					X	• Study intervention accountability is also performed at the Day 10 visit if the participant administered treatment after the Day 5 visit was conducted. • Provide dosing log on Day 1 and collect dosing log at end of treatment (Day 5 or Day 10).
Retrieval of unused study intervention					X	X					X	• Collect unused study intervention at the next visit after the last dose was taken. For example, if subsequent doses after the Day 5 visit are taken to reach a total of CCI doses, the unused study intervention, including the bottle, are collected at the Day 10 visit.
Prior/concomitant treatment(s)		X	X	X	X	X	X	X	X	X	X	• All prescription and over-the-counter medications including vaccines taken by the participant within 30 days before study entry (considered prior treatment) will be recorded. • RSV vaccinations and monoclonal antibody or antiviral treatment for the treatment of RSV at any time prior to the planned first dose will also be recorded. • Any therapies causing active immunosuppression will be also recorded.

Table 1. Study Schedule of Activities

Visit Identifier Abbreviations may be found in Appendix 11. X = required	Pre-screen (Optional)	Screen	Treatment Period			F/U					Early Discont.	Notes
			Day 1	Day 3	Day 5	Day 10	Day 15	Day 28	Day 35	Unplanned Visit for Post-Treatment ARI (in-person)		• Day relative to start of study intervention (Day 1). • Day 35 visit may be performed either in person or as a phone contact.
Visit Window	**Day -4 to 1**	**Day -1 to 1**	**(0)**	**(±1)**	**(+1)**	**(± 1)**	**(± 2)**	**(± 2)**	**(± 2)**	**Day 6 to 28**		• See Section 8.4.3 for follow-up AE and SAE assessments.
												• See Section 6.9 for additional information.
Patient Reported Outcomes												
EQ-5D-5L			X	X	X	X	X	X				• Baseline questionnaire should be administered before taking the study treatment. • See Section 8.2.8.1 for details.
Study Procedures and Assessments												• See Section 6 for additional information
Record RSV related medical visits and hospital admissions				X	X	X	X	X	X	X	X	• RSV related medical visits and hospital admissions a participant has had since the last assessment will be collected. Medical visits include those provided by a health care professional (HCP): outpatient or inpatient visit, emergency room or urgent care visit. • See Section 8.2.1.
Record/update household characteristics			X	X	X	X	X	X		X	X	• See Section 8.2.9.
Record oxygen support details			X	X	X	X	X	X		X	X	• See section 8.2.6.
Survival status								X	X		X	• See Section 8.2.2.
Record data to enable real world data collection for long-term follow-up (US only)								X				• For participants who provide optional informed consent. • See Section 10.10.1.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	• See Section 8.4 for additional information.

2. INTRODUCTION

Sisunatovir (PF-07923568, formerly RV521) is a potent inhibitor of RSV F protein mediated fusion that is currently being investigated as a treatment of adults with naturally acquired RSV infection who are at increased risk of developing severe illness. Additional studies are being conducted to evaluate sisunatovir as a treatment of RSV infection in pediatric patients.

2.1. Study Rationale

Currently there are no approved oral treatments for RSV, and patients that progress to severe illness are hospitalized and offered supportive care only [1]. The purpose of the study is to evaluate the efficacy and safety of sisunatovir in preventing severe clinical outcomes, including development of LRTI, hospitalization and death, in an adult population of naturally infected RSV participants with risk factors for severe illness, defined here as older age, chronic lung disease, heart failure, or a compromised immune system. The study will also evaluate the impact of sisunatovir on changes in RSV viral load that is obtained from nasopharyngeal samples.

2.2. Background

RSV belongs to the recently defined *Pneumoviridae* family, Orthopneumovirus genus [2,3]and was discovered more than 60 years ago [4] RSV has since been recognized as one of the most common causes of acute respiratory tract infections in adults. RSV is a major cause of morbidity and mortality among children [5], elderly people, people with cardiopulmonary comorbidities (such as COPD, asthma, or congestive heart failure), and individuals with a compromised immune system [6,7].An estimated 1.5 (95% CI 0.3 to 6.9) million episodes of RSV-related acute respiratory illness occurred in older adults in industrialized countries worldwide in 2015, and of these episodes approximately 14.5% involved a hospital admission. Globally, an estimated 14,000 in-hospital deaths in 2015 were associated with RSV-related acute respiratory illness [8]. Adults infected with RSV can have variable clinical findings that range in severity from mild respiratory symptoms to severe LRTI. Host immunity to RSV diminishes over time and can lead to recurrent infections [9].

At present, two adult RSV vaccines have regulatory approval in some countries to prevent progression to severe illness. However, no specific treatment with antivirals is available for patients who acquire the infection, other than aerosolized ribavirin [1]. Ribavirin, a nucleoside analogue, is the only licensed antiviral for the treatment of RSV in pediatric patients , but clinical use is restricted due to its limited antiviral potency, delivery route, toxicity, and teratogenic potential [10,11]. There is, thus, an unmet need for more targeted and better tolerated antivirals.

Sisunatovir (PF-07923568) is a novel, oral, potent inhibitor of RSV F protein mediated fusion and exerts antiviral activity against RSV by inhibiting viral entry into host cells. In this way, F protein inhibition may reduce both viral replication and pathology, reducing the severity of RSV related clinical outcomes. Thus, sisunatovir may provide clinical benefit to adult participants with RSV disease.

The sisunatovir preclinical profile, as well as the efficacy, safety and tolerability data from the initial human studies that are summarized in this protocol, provide a strong rationale for the clinical development of sisunatovir.

2.2.1. Nonclinical Pharmacology

See the current IB for further details.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In animal pharmacokinetic studies sisunatovir showed prolonged T_{max}, moderate-high CL, high volume of distribution, and oral bioavailability of 46%, 42-132%, and 63% in mouse, rat, and dog, respectively.

Plasma protein binding of sisunatovir was low to moderate across species, with average fraction unbound of CCI in human, mouse, rat, dog and guinea pig, respectively. Sisunatovir showed extensive distribution to the lung in studies of rats.

Sisunatovir is a substrate of CCI and is metabolized primarily by CCI.

Sisunatovir was evaluated for potential inhibition of CYPs and transporters in vitro. Overall, the primary DDI risks for sisunatovir are CCI and potential risk for CCI.

See the current IB for further details.

2.2.3. Nonclinical safety

CCI

See the current IB for further details.

2.2.4. Clinical Overview

To date, 9 clinical studies of sisunatovir have been completed; a total of 264 healthy adult participants and 41 pediatric patients with RSV-LRTI received sisunatovir in these studies. Key design features of the completed clinical studies are provided in the IB and summaries of the key clinical pharmacology, clinical efficacy and clinical safety data from the completed studies are provided in the sections below.

C5241002 is an RSV challenge study where 66 healthy adult male and female volunteers were inoculated with challenge virus. After the first positive PCR test from a nasal wash or after 5 days (whichever occurred first), participants were randomized 2:1 to receive sisunatovir, either at the dose of 200 mg or 350 mg q12h, or placebo for 5 days. The primary objective of the study was to assess the antiviral activity of sisunatovir versus placebo from nasal wash samples by RT-PCR from pre-dose until discharge at Day 12. Other objectives were related to clinical outcomes such as production of nasal discharge and presence and duration of RSV related symptoms, assessed through a symptom score model. Treatment with sisunatovir 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. Results for the AUC of total symptom score were consistent with the viral load AUC. Geometric mean AUCs of total symptom score were 195.56, 30.79 and 31.76 hours x score for placebo, 200 mg sisunatovir and 350 mg sisunatovir, respectively. The reduction in AUCs of total symptom score compared with placebo was statistically significant for both sisunatovir treatment groups; p=0.009 (84.26%) and p=0.002 (83.76%), (Wilcoxon Rank Sum test) for the 200 mg and 350 mg sisunatovir dose groups, respectively. Sisunatovir treatment resulted in a statistically significant reduction in the total weight of nasal discharge compared with placebo. Least squares mean

daily nasal mucus weight was significantly lower with sisunatovir 200 mg and 350 mg versus placebo (0.33 g, p=0.038 and 0.27 g, p=0.010, versus 0.61 g).

There are 7 ongoing studies:

- A Phase 1 multiple site study (C5241012) to assess the effects of hepatic impairment on the pharmacokinetics of sisunatovir.
- A Phase 1 single site study (C5241013) to assess the relative bioavailability of sisunatovir following single oral dose of different formulations under fed and fasted conditions in healthy adult participants.
- A Phase 1 multiple site study (C5241016) to assess the effects of renal impairment on the PK of sisunatovir.
- A Phase 1 single site study (C5241017) to assess the effects of a proton pump inhibitor on the PK of sisunatovir in healthy adult participants.
- A Phase 1 single site study (C5241018) to assess the PK, safety, and tolerability following single and multiple doses of sisunatovir in Chinese healthy adult participants.
- A Phase 1b multiple site study (C5241009) to assess the safety, tolerability, and PK of sisunatovir in pediatric participants up to age 60 months with RSV LRTI.
- A Phase 2/3 multiple site study (C5241007) to investigate efficacy and safety of oral sisunatovir compared with placebo in non-hospitalized symptomatic adults with RSV infection who are at risk of progression to severe illness.

In adult studies, the administration of sisunatovir was well tolerated at all doses, dosage forms and dosing regimens tested and the occurrence of TEAEs considered related to sisunatovir has been low. The most commonly reported treatment related TEAEs in adults were in the GI disorders System Organ Class: nausea, diarrhea and abdominal pain. These TEAEs have been mild to moderate in intensity and resolved without sequelae.

As of 20 January 2024, there were no SAEs attributable to sisunatovir and no deaths in the clinical studies. There has been 1 serious AE of fever reported in the pediatric study (C5241003) in a child hospitalized with RSV infection who received a single dose of sisunatovir. This was considered serious because it prolonged hospitalization, but the SAE was reported as not related to IMP. In C5241002 there was 1 SAE of sub-acute myocarditis reported for a subject on placebo; this was considered to be causally related to the challenge virus.

In adults, sisunatovir is slowly absorbed, reaching maximum plasma concentrations (T_{max}) at [redacted] hours with a half-life of [redacted] hours in healthy participants. Dosing to steady state resulted in steady state concentrations being reached after approximately [redacted] days of dosing

resulting in [redacted]-fold accumulation of exposure. AUC and C_{max} values [redacted] Following [redacted] days of dosing, the variability in PK parameters was [redacted] with %CV ranging from [redacted]% for C_{max} and [redacted]% for AUC_{12}.

For the [redacted] (C5241006) the extent of systemic exposure to sisunatovir (geometric mean AUC_{tau}) under fed and fasted conditions was [redacted] and [redacted] ng.h/mL on Day 1, respectively, and [redacted] and [redacted] ng.h/mL on Day 5, respectively. The between-participant variability was lower under fed conditions on Day 1 (CV [redacted]% compared with [redacted]%) and comparable between fed and fasted conditions on Day 5 (CV [redacted]% compared with 51%). Median T_{max} and mean terminal $t_{½}$ were comparable between fed and fasted conditions. Accumulation ratios were slightly higher in a fasted state, with R_{ac} and R_{ac},C_{max} being [redacted] and [redacted] and [redacted] and [redacted] in a fed state. Overall, plasma sisunatovir exposure based on AUC_{tau} and C_{max} were higher in the [redacted] group compared to the [redacted] group. This effect was more pronounced on Day 1. Test/Reference ratios of adjusted geometric means (90% CI) for AUC_{tau} and C_{max} were [redacted] and [redacted] on Day 1, and [redacted] and [redacted] on Day 5, respectively.

Preliminary results from [redacted] indicate that the tablet [redacted] The tablet administered [redacted] had a geometric mean (%CV) of [redacted] ng.hr/mL ([redacted]%) and [redacted] ng/mL ([redacted]%) for AUC_{inf} and C_{max}, respectively. The [redacted] administered under fasting conditions had a geometric mean (%CV) of [redacted] ng.hr/mL ([redacted]%) and [redacted] ng/mL ([redacted]%) for AUC_{inf} and C_{max}, respectively. [redacted]

Clinical DDI Study C5241004 demonstrated that the disposition of sisunatovir is affected by [redacted] Furthermore, sisunatovir was demonstrated to be a [redacted] so dose adjustments and increased monitoring for adverse effects for compounds that are [redacted] may need to be considered.

No participant in Study C5241001 had a QTcF interval change from baseline >30 msec. Furthermore, no significant QTc prolongation was detected in C-QT analyses performed in SAD participants (C5241001), MAD participants (C5241001), or DDI study participants (C5241004). The [redacted] demonstrated there was no [redacted] of the [redacted] at [redacted] of sisunatovir with [redacted]

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

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

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sisunatovir may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.4. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention(s) [Sisunatovir]	
Hepatobiliary system effects	CCI In completed clinical studies, mild transient asymptomatic elevations of liver enzymes have been observed in a few participants.	Safety monitoring including laboratory (ie, transaminases, GGT) and AE monitoring. Exclusion of patients with active liver disease or liver function impairment. (EC#9).
Gastrointestinal effects	CCI In completed adult clinical studies sisunatovir has been associated with mild to moderate GI AEs.	Participants will be closely evaluated to monitor for GI AEs.
Cardiovascular effects	CCI To date, Phase 1 studies in healthy participants and a study in pediatric participants has not shown clinically significant changes in safety laboratory parameters (including troponin in C5241001), ECGs and vital signs related to sisunatovir. A CCI was conducted to assess the effect of sisunatovir on QT interval. There was CCI of the CCI at CCI of sisunatovir with CCI	Monitoring will include vital signs, including heart rate, and baseline and for cause ECG assessments.

2.4.1. Benefit Assessment

In the virus challenge study, sisunatovir was found to significantly reduce the nasal RSV viral load in healthy volunteers, with consequent early recovery of symptoms. These findings may translate to direct clinical benefit in patients who acquire the infection naturally and are at increased risk of developing severe illness, due to the presence of older age, cardiopulmonary comorbidities and compromised immune system.

Participation in this study may also lead to improved knowledge about RSV and help develop new treatments that could benefit society.

Frequent medical evaluations, vital signs collection, blood tests and other assessments may also lead to improved health outcomes for participants.

2.4.2. Overall Benefit/Risk Conclusion

Considering the high prevalence of RSV, its potential negative impact on the morbidity and mortality of individuals at increased risk of severe illness and the financial burden on the health systems worldwide, taken together, the expected benefits of receiving sisunatovir for the treatment of RSV outweigh the risks of trial participation and those associated with the potential toxicity of sisunatovir identified in the early stage of development.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

All objectives, endpoints, and estimands will be evaluated in non-hospitalized adults who are infected with RSV and are at high risk of severe illness. The treatment effect is evaluated in the population of study participants who are randomized and treated irrespective of their compliance to the planned course of treatment or use of concomitant medications (see Section 9.1.1). The primary analysis and key secondary analyses are conducted in adults with confirmed RSV infection.

Objectives	Endpoints	Estimands
Primary:		
• To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with RSV-related hospitalization or death from any cause through Day 28.	• The difference in treatment proportions of patients experiencing RSV-related hospitalization or death from any cause through Day 28.
Key Secondary:		
• To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28.	• The difference in treatment proportions of patients experiencing RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28. A hospital visit of any duration will be included.
	• Proportion of participants with progression of LRTI through Day 10.	• The difference in treatment proportions of patients with progression of LRTI through Day 10 will be evaluated in the population of participants who do not

Objectives	Endpoints	Estimands
		have RSV-related severe LRTI (sLRTI-RSV) at randomization.
	• Proportion of participants with development of LRTI through Day 10.	• The difference in treatment proportions of patients who develop sLRTI-RSV or nsLRTI-RSV through Day 10 will be evaluated in the population of participants who do not have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Proportion of participants with resolution of LRTI at Day 15.	• The difference in treatment proportions of patients with resolution of LRTI at Day 15 will be evaluated in the population of participants who have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Mean number of days alive and free from hospital stay (hospital-free days) through Day 28.	• The difference in treatment means of number of days alive and free from hospital stay (hospital-free days) through Day 28.
Other Secondary:		
• To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with progression of LRTI through Day 3, 5, 15, and 28.	• The difference in treatment proportions of patients with progression of LRTI through Day 3, 5, 15, and 28 will be evaluated in the population of participants who do not have sLRTI-RSV at randomization.
	• Proportion of participants with development of LRTI through Day 3, 5, 15, and 28.	• The difference in treatment proportions of patients who develop sLRTI-RSV or nsLRTI-RSV through Day 3, 5, 15, and 28 will be evaluated in the population of participants who do not have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Proportion of participants with resolution of LRTI at Day 3, 5, 10, and 28.	• The difference in treatment proportions of patients with resolution of LRTI at Day 3, 5, 10, and 28 will be evaluated in the population of participants who have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28.	• The difference in treatment proportions of patients with improvement in LRTI status at Day 3, 5, 10, 15, and 28 will be evaluated in the population of participants who have sLRTI-RSV or nsLRTI-RSV at randomization.
	• Number of RSV related days in hospital through Day 28. • Number of RSV related days in ICU through Day 28.	• The difference in treatment means of number of RSV related days in hospital and separately, number of RSV related days in ICU, through Day 28.
	• Proportion of participants with a clinical response of Improvement or Resolution at Day 5, 10, 15, and 28.	• The difference in treatment proportions of patients with Improvement or Resolution at Day 5, 10, 15, and 28.

Objectives	Endpoints	Estimands
• To compare NP viral load changes among non-hospitalized adults at high risk for severe illness treated with sisunatovir relative to placebo.	• Proportion of participants with undetectable RSV viral load at each study visit through Day 28. • Change from baseline in RSV viral load at each study visit through Day 28.	• The difference in treatment proportions of patients with undetectable RSV viral load at each visit through Day 28 • The difference in treatment means of change from baseline in RSV viral load at each study visit through Day 28.
• To describe the safety and tolerability of sisunatovir relative to placebo among non-hospitalized adults at high risk for severe illness.	• Proportion of participants with TEAEs through Day 35. • Proportion of participants with SAEs through Day 35.	• NA.
• To determine the PK of sisunatovir among non-hospitalized adults at high risk for severe illness.	• Plasma concentrations of sisunatovir at steady state (Day 3 or later).	• NA.
Tertiary / Exploratory		
• To describe treatment emergent resistance to sisunatovir or fusion inhibitor class and its impact on viral load and clinical outcomes.	• Proportion of participants with post baseline changes in RSV F gene sequence that confer resistance to sisunatovir or fusion inhibitor class. • Change from baseline in viral load in participants with or without changes in RSV F gene sequence that confer resistance to sisunatovir or fusion inhibitor class. • Proportion of participants with RSV-related hospitalization or death from any cause through Day 28, in participants with and without post baseline changes in RSV F gene sequence that confer resistance to sisunatovir or fusion inhibitor class.	• NA.
• To describe changes in patient reported outcomes between sisunatovir and placebo arms.	• Change from baseline at Day 3, 5, 10, 15 and 28 in EQ-5D-5L scale.	• NA.
• To explore RSV recurrence in the sisunatovir and placebo arms.	• Proportion of participants with RSV recurrence at Day 10, 15 and 28.	• NA.
• To describe onward transmission in households between sisunatovir and placebo arms.	• The proportion of household contacts with confirmed or suspected ARI (symptomatic transmission) through Day 3, 5, 10, 15, and 28. • The proportion of household contacts who become infected with confirmed RSV (virological transmission) through Day 3, 5, 10, 15, and 28.	• NA.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2/3, superiority, adaptive parallel-arm, randomized, multi-center, placebo-controlled, double-blind study. Approximately 2375 symptomatic adult participants with RSV infection, who are at increased risk of progression to severe illness, will be randomized 1:1 to receive either oral sisunatovir CCI mg CCI , or matching placebo for 5 days (CCI doses). Randomization will be CCI status at baseline.

Sample size calculations determined that CCI randomized participants are required using the primary endpoint RSV related hospitalization and all-cause mortality. Assuming a CCI the required total sample size for the primary analysis will be increased to approximately CCI participants. Assuming CCI , and thus will not be included in the primary analysis, the planned total number of participants to be randomized will be increased to approximately 2375. However, study enrollment will be stopped after approximately CCI participants are available for the primary analysis. PK samples at additional timepoints will be collected from approximately CCI participants CCI to inform the population PK model.

- Enrollment of participants with CCI (new onset or worsening of chronic signs and/or symptoms) at randomization will be limited to approximately CCI %.
- Enrollment of participants CCI with none of the other risk factors will be limited to approximately CCI % .

Interim analyses:

- Efficacy IA 1: a planned interim analysis for futility will be done after approximately 45% of participants in the primary analysis set complete Day 28 assessments or have discontinued the study
- Efficacy IA 2: a planned interim analysis for early efficacy and futility with a sample size re-assessment will be done after approximately 65% of participants in the primary analysis set complete Day 28 assessments or have discontinued the study.
- PK IA: a planned PK IA to evaluate steady-state exposures, including $C_{troughSS}$, will be done after at least 100 participants randomized (approximately 50 participants in the PK concentration population) have completed the Day 5 PK assessments.

A sample size re-assessment will take place during the second efficacy IA with potential for an increase of up to CCI of approximately CCI

If futility or early efficacy are demonstrated at either of the efficacy IAs, the E-DMC

recommendations will be reviewed by the Sponsor Management Committee and a determination will be made regarding continuation or cessation of randomization into the study.

The total study duration is up to 5 weeks and includes a screening period of 1-2 days where randomization (Day 1) must occur by the second consecutive day, study intervention administration through Day 5, efficacy outcome assessments through Day 28, and a safety follow-up period through Day 35.

An external data monitoring committee (E-DMC) will review blinded and unblinded data to ensure the safety of participants on an ongoing basis throughout the entire duration of the study. The E-DMC will also review data from each of the two planned efficacy IAs, as specified in the E-DMC Charter.

When the PK IA is performed, an internal, independent, unblinded review committee separate from the study team will review population PK model-derived plasma concentration-time curves and PK parameters for sisunatovir. No safety or efficacy data will be used to inform the PK IA.

Participants in the United States will be invited to participate in optional, additional research using real world data to describe long-term health outcomes and healthcare utilization (see Section 10.10.1).

4.2. Scientific Rationale for Study Design

The choice of the current study design (randomized, double blind, superiority with 2 parallel arms) allows for a direct and unbiased statistical comparison between sisunatovir and placebo groups.

4.2.1. Rationale for end point selection.

The primary end point of hospitalization, defined as ≥24 hours of acute care in a hospital or similar acute care facility, or death by Day 28 reflects the poor clinical outcomes experienced by patients that progress to severe illness, and it has been agreed in consultation with regulatory agencies.

Secondary end points of LRTI and medically attended visits have been selected based on evidence from medical literature of disease progression and burden on health systems globally.

4.2.2. Rationale for Study Population

The population includes adult individuals with cardiopulmonary comorbidities and compromised immune system and older adults who are described in the medical literature as being at increased risk of hospitalization and death and in most need for safe and effective treatments.

Selection of participants with a symptom duration of ≤5 days is being implemented due to early data from clinical trials of other RSV F protein inhibitors in development [12,13].

4.2.3. Diversity of Study Population

The diversity strategy will include sites with the potential to support the recruitment of diverse populations across geographically diverse countries. Reasonable attempts will be made to enroll participants that are representative of the patient population that will be treated with sisunatovir in clinical practice.

4.2.4. Rationale for Comparator

Placebo will be used in this trial as a comparator to allow for an unbiased evaluation of the safety and efficacy of sisunatovir. The use of placebo is justified by the lack of approved RSV specific treatments.

4.2.5. Rationale for Adaptive or Novel Study Design

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of RSV related hospitalization or death in the primary analysis population, and about the treatment effect of sisunatovir. The planned efficacy IAs (including sample size re-assessment) allow for early stopping of the trial due to futility or early efficacy or allow for increasing the sample size.

4.2.6. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for sisunatovir, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required for female participants of childbearing potential (see SoA and Section 10.4).

4.3. Justification for Dose

To investigate the effect of sisunatovir on clinical activity following RSV infection, a viral challenge clinical study in healthy adult participants was conducted where doses of 200 mg or 350 mg q12h x 5 days were administered following confirmation of an RSV infection post inoculation (C5241002). While there was not a clinically meaningful difference between 200 and 350 mg sisunatovir (see Section 2.2.4), an increased incidence of GI AEs was observed at the 350 mg dose relative to the 200 mg dose, under fasting conditions. Higher rates of GI AEs were also observed at higher doses within the Phase 1 program (in the fasted state). A population exposure-safety model of sisunatovir indicates administration of the CCI mg dose has a lower probability of experiencing CCI (CCI%), CCI (CCI%), and CCI (CCI%), as compared to the CCI mg dose CCI%, CCI%, and CCI%, respectively). Additionally, administration of CCI mg under fed state reduces the probability of experiencing CCI CCI vs CCI%). Preliminary results from C5241006 demonstrated that the CCI mg CCI sisunatovir dose under fed conditions resulted in exposure above NOAEL limits, whereas exposures associated with CCI mg CCI fasting and fed were consistent with those observed in previous studies. Based on these findings, the CCI mg CCI dose that was found to

maximize efficacy while maintaining safety, tolerability and exposures below NOAEL will be evaluated in this study. To validate the proposed dose regimen in adults, a viral dynamics QSP model was developed from in vitro Plaque Assay EC_{90} data informing Clinical EC_{90}, sisunatovir PK informing clinical exposure, and viral challenge data informing viral dynamics. Simulations indicated that there was no additional benefit of loading doses or more than 5 days of treatment on reduction of viral load AUC. Additionally, doses below CCI mg were predicted to have attenuated reduction of viral load AUC.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled visit (Day 35) of the last participant in the study or the last scheduled procedure shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled visit (Day 35) shown in the SoA.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants aged 18 years or older (or the minimum age of consent, if above 18, in accordance with local regulations) at screening.

    - Women of childbearing potential must agree to use highly effective contraception. Refer to Appendix 4 (Section 10.4.3 and 10.4.4) for reproductive criteria for female participants.

Disease Characteristics:

2. Diagnosis of RSV infection, as determined by a positive RT-PCR, rapid antigen test, or other locally available diagnostic test in any respiratory specimen (eg, nasal,

nasopharyngeal swab, sputum) collected within 5 days of randomization. Randomization must occur no later than the 5th day since the diagnosis of RSV infection where the day of RSV diagnosis is the 1st day.

3. New onset or worsening (if present chronically) of at least one of the following signs and/or symptoms consistent with a viral acute respiratory infection (ARI), within 5 days prior to randomization: nasal congestion, nasal discharge, sore throat, cough, sputum production, shortness of breath, or wheezing. Randomization must occur no later than the 5th day, where the day of onset/worsening is the 1st day.

Other Inclusion Criteria:

4. Has at least 1 of the following characteristics or underlying medical conditions:

   - 65 years of age or older.
   - Chronic lung disease that is symptomatic or requiring treatment, including but not limited to: COPD, asthma, CF, PF, PAH, alpha-1 anti-trypsin deficiency, or pulmonary sarcoidosis.
   - Heart failure (functional class II-IV according to NYHA classification).
   - Immunosuppressive disease or condition (eg, hematological malignancy, CAR-T, bone marrow or organ transplant recipient, primary immune deficiency, or HIV infection with CD4+ cell count <200 / μL within the last 6 months) OR use of at least 1 of the following immune-weakening medications:
     - Recent treatment with corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days, all of which must have been within the last 30 days prior to study entry OR are currently receiving ≥20 mg daily that must have been administered for at least 14 consecutive days at the time of study entry.
     - Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, TNF blockers, or other highly immunosuppressive drugs such as biologics (eg, ustekinumab, anti-CD20).

5.2. Exclusion Criteria

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

Medical Conditions:

1. Any medical (eg, confirmed concurrent active systemic infection other than RSV including bacterial, fungal, or viral) or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the

participant inappropriate for the study or interfere with the evaluation of response to the study intervention.

2. Diagnosis of viral respiratory infections other than RSV including influenza and SARS-CoV-2, within 7 days of randomization. A negative test for SARS-CoV-2 and influenza is required within 7 days of randomization.

3. Current need for hospitalization or anticipated need for hospitalization for any reason to provide inpatient/acute care within 24 hours after randomization in the clinical opinion of the site investigator.

4. Any clinically significant ECG abnormality in the pre-dose ECG that, per investigator judgement, may affect participant safety.

Prior/Concomitant Therapy:

5. Current or recent use of any prohibited concomitant medication(s) that may result in a clinically significant drug-drug interaction (see Section 10.9 for details).

6. Use of oral or inhaled ribavirin in prior 30 days or anticipated use during the study.

Prior/Concurrent Clinical Study Experience:

7. Prior administration of study drug in a sisunatovir trial, recent administration of an investigational drug or vaccine (within 30 days or 5 half-lives), or concurrent participation in a study of another investigational drug or vaccine.

Diagnostic Assessments:

8. Renal impairment defined by an eGFR <30 mL/min/1.73 m^2 or receiving dialysis.

9. Active liver disease with AST or ALT >3 ULN, Total bilirubin ≥2 × ULN (For Gilbert's syndrome, direct bilirubin >ULN is exclusionary) within the past 3 months, or liver function impairment with Class B or C per Child Pugh classification.

Other Exclusion Criteria:

10. Has hypersensitivity to or other contraindication to any of the components of the study interventions, as determined by the investigator.

11. 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

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 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 the 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.

5.4. Pre-screening consent and pre-screening viral testing (optional, if applicable)

Some patients with ARI who are at risk of progression to severe illness may not have routine medical access to rapid RSV testing. For these patients, access to a rapid RSV test would help determine if this patient may be eligible to enroll in this clinical study and an optional pre-screening visit may be conducted. Once pre-screening informed consent is obtained, a sponsor-supported pre-screening viral test will be performed. In addition to testing for RSV, the pre-screening viral test may also test for SARS-CoV-2 and/or influenza.

Participants must meet all of the following criteria to be eligible for a pre-screening visit:

- Participant has not undergone an RSV test for this ARI episode.
- Participant is aged 18 years or older (or the minimum age of consent, if above 18, in accordance with local regulations).
- New onset or worsening (if present chronically) of at least one of the following signs and/or symptoms consistent with a viral ARI, within 5 days of pre-screening: nasal congestion, nasal discharge, sore throat, cough, sputum production, shortness of breath, or wheezing. If the study meets the [redacted]% enrolment limit for patients randomized 5 days from symptom onset, then the above criteria will be limited to within 4 days of symptom onset.

- Has at least 1 of the following characteristics or underlying medical conditions:
  - 65 years of age or older. If the study meets the [redacted]% enrolment limit for participants ≥65 years of age with none of the other risk factors that are listed as inclusion criteria, then the age criterion alone can no longer be used to determine eligibility for pre-screening viral testing.
  - Chronic lung disease that is symptomatic or requiring treatment, including but not limited to: COPD, asthma, CF, PF, PAH, alpha-1 anti-trypsin deficiency, or pulmonary sarcoidosis.
  - Heart failure (functional class II-IV according to NYHA classification).
  - Immunosuppressive disease or condition (eg, hematological malignancy, CAR-T, bone marrow or organ transplant recipient, primary immune deficiency, or HIV infection with CD4+ cell count <200 / µL within the last 6 months) OR use of at least 1 of the following immune-weakening medications:
    - Recent treatment with corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days, all of which must have been within the last 30 days prior to study entry OR are currently receiving ≥20 mg daily that must have been administered for at least 14 consecutive days at the time of study entry.
    - Active treatment causing significant immunosuppression, including alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, TNF blockers, or other highly immunosuppressive drugs such as biologics (eg, ustekinumab, anti-CD20).

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened for 30 days (ie, they may be rescreened during the following RSV season if they represent with a new infection).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

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

6.1. Study Intervention(s) Administered

Study Interventions		
Intervention Name	Sisunatovir CCI mg	Placebo
Type	Drug	Drug
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	100 mg	0 mg
Dosage Level(s)	CCI mg CCI	Placebo for CCI mg CCI
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement. Blinded.	Study intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement. Blinded.
SRSD	IB	NA
Current/Former Name(s) or Alias(es)	RV521, PF-07923568	Placebo

Study Arm(s)		
Arm Title	Sisunatovir	Placebo
Arm Description	Participants will receive CCI tablets of 100 mg of sisunatovir CCI from Day 1 to Day 5 (CCI doses)	Participants will receive CCI matching placebo tablets CCI from Day 1 to Day 5 (CCI doses).

6.1.1. Administration

Participants will be dispensed 1 bottle of sisunatovir or matching placebo. Participants will take CCI tablets of sisunatovir or matching placebo every CCI (dose of CCI mg; total daily dose of CCI mg) for a total of CCI doses (5 days or 6 days if only one dose was taken on Day 1).

Participants should take the first dose of study intervention on Day 1, preferably during the in-person visit or as soon as possible after randomization. To allow the participant to select a convenient CCI dosing schedule, timing of dosing for the second dose may be adjusted slightly but should be taken at least CCI but no later than CCI after the first dose. The remaining doses should be taken every CCI

Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. Participants should take the study intervention CCI [redacted] Refer to the IP Manual for additional dosing and administration instructions. Whether or not the participant had CCI [redacted] before taking study intervention will be collected.

If a dose is delayed, it should be taken as soon as possible, but no later than CCI [redacted] before the next scheduled dose. Participants should not double up the next dose of study drug to "make up" what had been missed. Dosing should be stopped at the end of the treatment period CCI [redacted] doses total). Any remaining tablets at the end of 5 days (or 6 days if only one dose was administered on Day 1) must be returned at the next study visit.

6.1.2. Medical Devices

Not applicable.

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 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 IPM or other specified location.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention. See the IPM for storage conditions of the study intervention.

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. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**

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

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using unique container numbers via an IRT system in the bottles provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed using an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Randomization will be CCI [redacted] at baseline (CCI [redacted]).

Study intervention will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

This is a double-blind study.

6.4.1. Blinding of Participants

Participants and their caregivers will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

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 until all participants complete the Day 35 visit (or early discontinuation prior to Day 35 visit).

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

6.4.3. Blinding of the Sponsor

The study will be unblinded after all participants complete the Day 35 visit (or early discontinuation prior to Day 35 visit) and analyses through Day 35, including the primary and key secondary efficacy endpoint analyses, will be conducted. Details of the unblinded sponsor staff supporting the E-DMC and the timing of unblinding will be outlined in the Unblinding Plan. The majority of sponsor staff will be blinded to study intervention allocation. A third-party designee will be unblinded to limit the number of sponsor staff that need to be unblinded. Limited sponsor staff independent of the study team may be unblinded to support the interactions with, and the unblinded analyses for, the E-DMC and regulatory authorities that may be required while the study is ongoing. For the efficacy IAs, sponsor staff will only be unblinded at the group level and not have access to individual participant assignments. For the PK IA, participant-level unblinding will be restricted to limited sponsor staff performing the PK IA who will be independent from the study and have no other responsibilities associated with the study.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. 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 attempt 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. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit as indicated in the SoA.

Participants will be issued a paper dosing log and will be trained how to record the date and time of study intervention dosing on Day 1. The participant will bring the paper dosing log to each study visit until the dosing log is collected after dosing is complete.

Site personnel will review the dosing log at site visits as indicated in the SoA. If any noncompliance with dosing entries is suspected or observed in the data, site personnel remind the participant of the relevant study procedures and/or entering the dosing information in the dosing log, as applicable.

Study intervention compliance and dose administration dates and times will be recorded in the CRF and will be assessed by delegated study personnel at study visits through counting returned tablets, reviewing the dosing log, and discussion with the participant, if applicable. A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records as source documentation. Deviation(s) from the prescribed dosage regimen should be recorded in source documents.

The following noncompliance cases will be considered medication errors and reported as protocol deviations (see Section 8.4.9):

- Participants missing study intervention for 2 consecutive doses.
- Participants who have an overall study intervention compliance <80% or >120%.

6.6. Dose Modification

Dose modifications are not permitted in this study.

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

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any single dose of sisunatovir greater than CCI mg or a daily dose greater than CCI mg within the first 24-hour time period will be considered an overdose. These doses were found to be well-tolerated, safe, and maintained exposures below the NOAEL in previous clinical studies.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 24 hours from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

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

6.9. Prior and Concomitant Therapy

Prohibited medications prior to the study:

Because the pharmacological induction effect on CCI lasts for about 14 days, any administration of a moderate or strong CCI inducer must have ended at least 14 days prior to randomization.

Similarly, considering that pharmacological inhibition of CCI enzyme wanes approximately 14 days after exposure to an inhibitor, any moderate or strong CCI inhibitor must have been discontinued at least 14 days before randomization (21 days for St John's wort).

Additionally, administration of CCI must have ended 5 days prior to randomization and administration of CCI must have ended at least 12 hours prior to randomization.

A non-exhaustive list of prohibited medications is included in Section 10.9.

Prohibited medications during the study:

Use of any concomitant medication that is either a strong or moderate inducer, or a strong or moderate inhibitor of CCI enzyme, and therefore may result in altered exposure of sisunatovir, is prohibited during the dosing period of the study.

Sisunatovir is a moderate inhibitor of CYP3A4 and may increase concentration of CYP3A4 substrates. Medications that are highly dependent on CYP3A4 for their clearance and have a narrow therapeutic index, and for which a potential life-threatening adverse effect may occur in case of higher exposure, are also prohibited.

Additionally, any administration of CCI is prohibited during the dosing period of the study. The use of CCI are not allowed within CCI study drug administration.

Use of a RSV vaccine is prohibited after randomization and during the period of the study.

A non-exhaustive list of prohibited medications is included in Section 10.9.

Permitted during the study:

Participants may receive concomitant medications, including standard of care for RSV infection, unless listed as prohibited medication according to the criteria outlined in Section 10.9.

Sisunatovir may be an inhibitor of CCI and CCI Medications that are dependent on CCI or CCI for their clearance, are permitted if the interaction is not considered clinically significant or if they can be dose adjusted, monitored or temporarily discontinued (eg, corticosteroids, statins, immunosuppressants) without posing additional risks to the participant.

Additionally, sisunatovir is a CCI inhibitor and therefore medications that are sensitive CCI substrates CCI will be permitted provided that the participants are appropriately monitored by the investigator who should be aware that the active investigational product (sisunatovir) may compete for the metabolism of such products, resulting in higher drug levels of these medications.

The use of CCI (such as CCI is allowed with CCI

A non-exhaustive list of medications that may be administered with caution is included in Section 10.9

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4 in Section 10.4).

Participants who received an RSV vaccine prior to randomization are eligible for enrollment.

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 where study intervention will be permanently discontinued include the following:

- AE of Grade 3 severity or greater and considered by the investigator to be related to the study intervention;
- SAE considered by the investigator to be related to the study intervention;
- Requirement for prohibited concomitant medication;
- Participant who becomes pregnant during the course of the study;
- Study terminated by the Sponsor;
- Withdrawal by participant or legally authorized representative;
- If post-screening eGFR falls to <30 mL/min/1.73 m^2 the participant will be instructed to discontinue any remaining study intervention doses as soon as study staff become aware of the eGFR results.
- If the participant is hospitalized, and none of the criteria above are met, study intervention may continue to be administered, as feasible, and based on the judgment of the investigator.

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for all subsequent planned assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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, further study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

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

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

Follow-up Assessments

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

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

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7 in Section 10.7.

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

Differentiating Acute Kidney Injury from DICI:

A confirmed Screat increase is defined as:

(i) ≥0.3 mg/dL (≥26.5 µmol/L) within prior 48 hours OR

(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

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

Adult Participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys

	AKI (including DIKI) **Any one of the below**	**DICI**
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 7 in Section 10.7) for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

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

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

7.1.2. Liver Injury

A participant who meets the criteria of potential DILI (Hy's law) case as described in Section 10.6 will be withdrawn from study intervention.

7.1.3. ECG Changes

A participant who meets either bulleted criterion based on ECG readings will be withdrawn from the study intervention.

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

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

7.1.4. Pregnancy

If a participant becomes aware of pregnancy during the study, they are to be discontinued from study intervention.

7.1.5. COVID-19 (SARS-CoV-2) and influenza

Participants will be tested for SARS-CoV-2 and influenza within 7 days of study randomization. If a participant develops an infection from influenza or SARS-CoV-2 through the course of the study, the investigator will decide whether to continue or permanently discontinue treatment with the study drug. If the patient's treatment requires a prohibited medication (eg, nirmatrelvir/ritonavir), the study drug must be discontinued. If a participant has SARS-CoV-2 or influenza during the study, this should be reported as an AE or SAE (as appropriate).

7.1.6. Temporary Discontinuation

Not permitted.

7.1.7. Rechallenge

Not permitted.

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;
- Study terminated by Sponsor;
- Withdrawal of consent by authorized legal representative.

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to attend 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.

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 wellbeing 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.

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 minimum total blood sampling volume for individual participants in this study is approximately 70 mL and 90 mL for the approximately CCI participants providing additional PK samples. Additional blood samples may be taken for safety or eligibility assessments at times specified in the SoA, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

Participants must have a positive RSV test before enrollment into the clinical study. RSV, SARS-CoV-2, and influenza diagnostic tests or other procedures conducted as part of the participant's standard of care and obtained before signing of the ICD may be utilized for eligibility review purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA. If a participant does not have access to obtain an RSV test, please see Section 5.4 for the pre-screening procedure informed consent option.

Participants in the United States will be invited to provide informed consent to participate in optional, additional research using real world data to describe long-term health outcomes and healthcare utilization (see Section 10.10.1)

8.1.1. Baseline Procedures

Medical history in addition to RSV disease history and demographics will be collected at screening. Smoking status will be collected.

Complete medication history of all prescription or nonprescription drugs (including vaccinations), and dietary and herbal supplements taken within 30 days prior to the planned first dose will be collected. RSV-related vaccinations and monoclonal antibody for the treatment or prevention of RSV at any time prior to randomization will also be collected. Medications causing ongoing immunosuppressant effect, such as biologics or cancer

treatments, administered at any time prior to randomization will be collected. Risk factors for the participant developing severe RSV illness will be recorded.

Viral Screening Assessment for Study Eligibility

If the participant fails to provide a negative test for SARS-CoV-2 and influenza within 7 days of randomization, a specimen will be collected at screening for viral testing of SARS-CoV-2 and/or influenza. Viral testing of SARS-CoV-2 and/or influenza will be performed according to the manufacturer information for use Some testing equipment will simultaneously test this nasal swab for RSV, and a negative RSV result from this test will exclude the participant from the study.

8.1.2. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described in the SoA.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.2. Efficacy Assessments

8.2.1. RSV-related hospitalizations and Medical Details

Details of participants' RSV-related medical visits (ie, hospitalization of any duration, urgent care, emergency room) will be collected during study visits, including level of care (ICU status), dates of utilization (including admission and discharge), and discharge status, as applicable.

For the primary endpoint, hospitalization of at least 24 hours of acute care is defined as ≥24 hours of acute care in a hospital or similar acute care facility. This includes specialized acute medical care unit within an assisted living facility or nursing home. Participants who are waiting in an emergency department or other hospital unit for an inpatient bed to become available are considered hospitalized provided that a decision to admit to inpatient care has occurred. For the secondary endpoint of RSV-related visits (urgent care/ED/hospital) or death from any cause, no minimum duration of hospitalization is required.

Investigators will determine if a medical visit is related to RSV. For reference, RSV related medical visits are those attendances that would not otherwise occur in the absence of the RSV infection. These may include visits for: deterioration or decompensation of the lung function that require supplemental oxygen; development of secondary respiratory tract infections that require antibiotic treatment; management of severe symptoms associated with RSV such as fever; worsening or decompensation of cardiac or renal function in patients with underlying cardiac or renal disease.

8.2.2. Survival status

Information about the death of a participant may be collected from death registries, hospital databases, other healthcare professionals, from participant's legal representatives, or other persons authorized by the participant and according to local regulations. The death of a participant cannot be assumed by their non-responsiveness, as the participant may be lost to follow-up.

8.2.3. Clinical response

Clinical response is evaluated by the investigator at Day 5, 10, 15, and 28 visits using the criteria for ARI in Table 2 that were required for study entry.

Table 2. Criteria for ARI

ARI is defined as the presence of 1 or more of the following signs and symptoms:
• New or increased nasal congestion.
• New or increased nasal discharge.
• New or increased sore throat.
• New or increased cough.
• New or increased sputum production.
• New or increased shortness of breath.
• New or increased wheezing.

The outcome of this assessment will be recorded in the CRF as one of the following categories:

- Resolution – All ARI signs or symptoms are absent or have returned to pre-infection status.
- Improvement – No new ARI signs or symptoms, and no worsening of existing signs or symptoms compared to the Day 1 visit. At least one sign or symptom (but not all) present at Day 1 is absent, improved or has returned to pre-infection status.
- No change – No change in the ARI signs or symptoms compared to the Day 1 visit.
- Worsening – New or worsening in severity of at least one ARI signs or symptom compared to the Day 1 visit.

8.2.4. RSV-related lower respiratory tract infection

Signs and symptoms of RSV will be collected by the Investigator per the SoA (Section 1.3) during scheduled visits. Criteria for diagnosis of LRTI are provided in Table 3. Criteria for diagnosis of severe LRTI (sLRTI) are provided in Table 4 [14]. Intensity grading displayed in Table 5 is a component of the severe LRTI criteria. An episode of LRTI that does not meet criteria for sLRTI is considered non-severe LRTI (nsLRTI). Investigators will determine if sLRTI or nsLRTI is related to RSV (referred to as sLRTI-RSV and nsLRTI-RSV).

- Development of LRTI is defined as transitioning from not having LRTI at randomization to having nsLRTI-RSV or sLRTI-RSV.
- Progression of LRTI is defined as development of LRTI or transitioning from nsLRTI-RSV at randomization to sLRTI-RSV.
- Resolution of LRTI is defined as transition from nsLRTI-RSV or sLRTI-RSV at randomization to not having nsLRTI-RSV and not having sLRTI-RSV.
- Improvement in LRTI status is defined as LRTI resolution or transition from sLRTI-RSV at randomization to nsLRTI-RSV.

Table 3. Criteria for LRTI

<table>
<tr><td colspan="2">LRTI is defined as:
• ≥2 lower respiratory signs or symptoms for at least 24 hours including at least 1 lower respiratory sign;
Or
• 3 lower respiratory symptoms for at least 24 hours.</td></tr>
<tr><td>Lower respiratory symptoms
• New or increased sputum.
• New or increased cough.
• New or increased dyspnea (shortness of breath).</td><td>Lower respiratory signs
• New or increased wheezing.
• New or increased crackles/ronchi based on chest auscultation.
• Respiratory rate ≥ 20 respirations/ minute.
• Low or decreased oxygen saturation (O_2 < 95% or ≤ 90% if pre-season baseline is < 95%).
• Need for new or increased oxygen supplementation.</td></tr>
</table>

Table 3. Criteria for LRTI

LRTI is defined as:
• ≥2 lower respiratory signs or symptoms for at least 24 hours including at least 1 lower respiratory sign; Or • 3 lower respiratory symptoms for at least 24 hours.

Criteria for LRTI are based on Papi, et al. 2023 [14].

Table 4. Criteria for severe LRTI

Severe LRTI is defined as the presence of LRTI with at least one of the following criteria:
• ≥2 lower respiratory signs. • An LRTI episode assessed as 'severe intensity' by investigator per intensity grading in Table 5. • Need for hospitalization. • Need for positive airway pressure therapy (eg, CPAP). • Need for other types of mechanical ventilation.
Lower respiratory signs:
• New or increased wheezing. • New or increased crackles/ronchi based on chest auscultation. • Respiratory rate ≥ 20 respirations/minute. • Low or decreased oxygen saturation (O_2 < 95% or ≤90% if pre-season baseline is <95%). • Need for new or increased oxygen supplementation.

Criteria for severe LRTI are based on Papi, et al. 2023[14].

Table 5. Intensity grading for LRTI

Mild intensity	An LRTI episode which is easily tolerated by the participant causing minimal discomfort and not interfering with everyday activities* or self-care**.
Moderate intensity	An LRTI episode which is sufficiently discomforting to interfere with everyday activities* but does not interfere with self-care**.
Severe intensity	An LTRI episode which prevents everyday activities* and interferes with self-care.**

Intensity grading for LRTI are based on Papi, et al. 2023 [14].
* Everyday activities include housework, work, family activities, or leisure activities. Interference in everyday activities must be due to signs and symptoms of the acute respiratory infection and note solely due to viral infection quarantining/isolation considerations.
**Self-care includes feeding, bathing, grooming, dressing, and toileting.
Change of everyday activities and self-care should be compared to each patient's baseline status. For example, a previously mobile participant becoming bed bound would be an example of severe LRTI.

8.2.5. Post-treatment ARI

Participants must meet criteria for ARI (as defined in Table 2 to be enrolled in the study. Any patient with a clinical response of Resolution (see Section 8.2.3) at Day 5, 10, or 15 that later experiences new or worsening of ARI symptoms lasting more than 1 day should contact the site staff or investigator to schedule an unplanned post-treatment ARI visit, which should optimally occur within 2 days after the onset of new or worsening symptoms. If the participant is scheduled to have a planned treatment visit or follow-up visit within 3 days of symptom onset of the recurrent ARI, then an unplanned study visit is not necessary.

The purpose of this visit is to perform a clinical assessment and collect a NP swab for virology assessment that can be used to evaluate potential recurrence of RSV infection.

8.2.6. Oxygen Support Details

Type of oxygen support (eg, oxygen supplementation received, mechanical ventilation or ECMO received in hospital) will be collected at baseline and subsequent visits.

8.2.7. Imaging Assessments

Unplanned imaging performed according to routine medical care will be recorded in the source document.

8.2.8. PRO Assessment

8.2.8.1. EQ-5D-5L

EQ-5D is a standardized, validated, generic health related quality of life questionnaire used in clinical and economic HTA evaluations. The questionnaire comprises five questions and covers dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Designed to be self-completed by respondents, the instrument takes a few minutes to complete and is intended to be cognitively undemanding [15-20].

The participant will be invited to complete the questionnaire on an electronic device at the site, and according to the SoA. The first questionnaire should be administered before taking the study drug. If assistance is required to help complete the questionnaire, the site staff should remain neutral and avoid leading participants towards specific answers.

In the suite of EQ-5D instruments developed, the most recent EQ-5D-5L has expanded to a 5-level scale of evaluation compared to the original 3 level evaluation scale. Validation has shown improved reliability and sensitivity of the EQ-5D-5L compared with the original in various diseases. The instrument retains utilities in assessing mobility, self-care, usual activities, pain/discomfort, anxiety/depression and health status using a VAS. The EQ-5D-5L should be completed as described in the SoA, with appropriate training to ensure appropriate measurement at baseline and to limit any potential influence on patient self-assessment during denoted site visits [15-20].

8.2.9. Household Characteristics

Household characteristics will be determined through interview with the participant and may be updated during the study. This assessment is exploratory in nature and will support the characterization of household transmission of acute respiratory infection. The household characteristics include:

- Number of people living in the household.
- Number of additional cases of confirmed or suspected acute respiratory infection among household contacts.
- Number of additional confirmed RSV positive household contacts.

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 general physical examination will be performed by a medically qualified individual (or other authorized delegate) at screening/baseline (see Table 1) and include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. Physical examinations conducted at subsequent study visits will be done at discretion of the investigator if the participant has symptoms that need to be evaluated. Investigators should pay special attention to any previously identified or new AE/targeted condition that the participant has experienced.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the

definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2. Vital Signs

Temperature, pulse rate, respiratory rate, oxygen saturation level, and blood pressure will be assessed as specified in Table 1.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3 in Section 10.3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed with the participant, in the supine or seated position with their feet on the floor, when possible, with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a semisupine or sitting position, in a quiet setting without distractions.

BP and PR will be taken before blood collection for laboratory tests and consist of a single measurement of PR and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute apart). The average of the 3 BP readings will be recorded on the CRF.

8.3.2.2. Temperature and Respiratory Rate

Temperature (oral, tympanic, axillary, or temporal artery), and respiratory rate, will be assessed and recorded in the CRF.

8.3.2.3. Oxygen Saturation

Oxygen saturation will be assessed as part of the vital signs assessment by a pulse oximeter and recorded in the CRF. Participants who are on chronic oxygen supplementation will be assessed whilst on supplementation.

8.3.3. Electrocardiograms

A single, standard 12-lead ECG will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. The ECG should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

A qualified medical provider should interpret the 12-Lead ECG used for screening prior to enrollment.

ECG data will be submitted to a central laboratory for measurement and interpretation. The final ECG report from the central laboratory 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 in Section 10.8) and should be evaluated further, as clinically warranted.

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

ECG values of potential clinical concern are listed in Appendix 8 in Section 10.8.

8.3.3.1. Alternative Facilities for Electrocardiograms

The participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results. ECGs can also be performed through remote device collection.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 (Section 10.2) 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 (Section 10.2), 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.

Laboratory safety parameters will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 [21]. 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 28 days of the last dose administration 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 (Section 10.6) for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 (Section 10.7) for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations may be conducted at a local laboratory, during a mobile visit, or at home if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology
- Biochemistry

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.5. Pregnancy Testing

A urine or serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA.

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 in Section 10.3.

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

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

During the active collection period as described in Section 8.3, each participant/legal guardian/legally authorized representative 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 (including the pre-screening informed consent document, if applicable), which is obtained before undergoing any study-related procedure and/or receiving study intervention, through Day 35.

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. For participants who provide pre-screening informed consent, the active collection period ends 30 minutes after collection of the pre-screening viral testing or once viral testing results become available, whichever occurs first.

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT AE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 in Section 10.3.

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 (Section 10.3).

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.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- 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.
- A male family member or healthcare provider who has been exposed to the study intervention by ingestion 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 or participant's partner, the investigator must report this information to Pfizer Safety using 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 a minimum of 28 calendar days after the last administration of study intervention.

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not yet proven in the study population and half of the participants are on placebo.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- Two consecutive missed doses;
- Participants who have an overall study intervention compliance ≤80% or ≥120%;
- 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.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of sisunatovir as specified in the SoA. Participants may be requested during any scheduled and unplanned treatment period visits to provide blood samples by venipuncture for PK analysis purposes. 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 obtained ≤1 hour outside the scheduled nominal sampling time windows 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. For the CCI participants with additional PK sampling timepoints, 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 classified as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of sisunatovir. Samples collected for analyses of sisunatovir 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. The data may be used for internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

Samples collected for measurement of concentrations of sisunatovir will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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 would 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.

8.6.2. Retained Research Samples for Genetics

Retained Research Samples will be collected in this study as specified in the SoA.

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow. Country-specific considerations are noted in Section 10.10.

Retained Research Samples may be used CCI [redacted]

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- NP swab samples will be collected to measure viral RNA levels by RT-PCR and includes an internal quality control for sample collection.
- NP swab sample will be used for pathogen panel screening.
- Residual NP swab samples will be used for viral sequencing.

CCI [redacted]

Respiratory Pathogen Assessments

A baseline NP swab sample (taken pre-dose) will be collected per the SoA and used to measure RSV RNA levels, viral sequencing and to assess for RSV and CCI [redacted]

CCI [redacted] at a central lab. These tests will not be used to determine study eligibility or for real-time clinical oversight.

Additional NP swab samples will be collected per the SoA and will be analyzed to measure RSV RNA levels and will be used for viral sequencing to evaluate potential genetic viral variants.

CCI [redacted]

Residuals of all samples may be retained beyond the end of the study to enable the analyses described above and related biomarker research on the study intervention and disease, if sufficient samples are available. Storage and shipping instructions will be in accordance with the laboratory manual.

8.7.1. Pharmacodynamic Biomarkers

Pharmacodynamic biomarker research will not be conducted in this study.

8.7.2. Specified Gene Expression (RNA) Research

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

8.7.3. Specified Protein Research

CCI [redacted] will be collected, as specified in the SoA, CCI [redacted]. Analysis may include but is CCI [redacted]. Residuals of all samples may be stored and used for additional analyses related to RSV and/or the mechanism of action of sisunatovir.

Details on processes for collection and shipment of these samples can be found in the laboratory manual and supporting documents.

8.7.4. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.5. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

CCI [redacted]

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA. Country-specific considerations are noted in Section 10.10.

Retained Research Samples may be used [redacted]

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in laboratory manual.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Several study endpoints, such as number of days spent in hospital or number of medically attended visits can be used to characterize healthcare resource utilization and health economic parameters.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The primary hypothesis to be tested is whether sisunatovir is superior to placebo in proportion of participants with RSV-related hospitalization (as defined in Section 8.2.1) or death from any cause through Day 28. The statistical hypothesis is as follows:

$$H_0: \pi_{sisunatovir} - \pi_{placebo} = 0 \text{ vs.}$$

$$H_1: \pi_{sisunatovir} - \pi_{placebo} < 0$$

Where $\pi_{sisunatovir}$ and $\pi_{placebo}$ are the proportion of participants with RSV- related hospitalization or all-cause death through Day 28.

Hypotheses for key secondary endpoints are similar, based on proportions or means as applicable.

9.1.1. Estimands

9.1.1.1. Primary Estimand

The primary estimand is defined by the following attributes:

Population: non-hospitalized adults who are infected with RSV and are at high risk of severe illness.

Endpoint: Proportion of participants with RSV-related hospitalization or death from any cause through Day 28.

Treatment condition: the randomized treatment (sisunatovir or placebo).

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death directly into the endpoint.

Population-level summary: difference in proportions between treatments.

9.1.1.2. Secondary Estimands

Key Secondary Estimands

The first key secondary estimand is defined by the following attributes:

Population: non-hospitalized adults who are infected with RSV and are at high risk of severe illness.

Endpoint: Proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28.

Treatment condition: the randomized treatment (sisunatovir or placebo).

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death directly into the endpoint.

Population-level summary: difference in proportions between treatments.

The second key secondary estimand is defined by the following attributes:

Population: non-hospitalized adults who are infected with RSV and are at high risk of severe illness, who at randomization have either no LRTI or only nsLRTI-RSV.

Endpoint: Proportion of participants with progression of LRTI through Day 10.

Treatment condition: the randomized treatment (sisunatovir or placebo).

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered progression of LRTI.

Population-level summary: difference in proportions between treatments.

The third key secondary estimand is defined by the following attributes:

Population: non-hospitalized adults who are infected with RSV and are at high risk of severe illness, who at randomization have no LRTI.

Endpoint: Proportion of participants with development of LRTI through Day 10.

Treatment condition: the randomized treatment (sisunatovir or placebo).

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered development of LRTI.

Population-level summary: difference in proportions between treatments.

The fourth key secondary estimand is defined by the following attributes:

Population: non-hospitalized adults who are infected with RSV and are at high risk of severe illness, who at randomization have either nsLRTI-RSV or sLRTI-RSV.

Endpoint: Proportion of participants with resolution of LRTI at Day 15.

Treatment condition: the randomized treatment (sisunatovir or placebo).

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered "not resolved".

Population-level summary: difference in proportions between treatments.

The fifth key secondary estimand is defined by the following attributes:

Population: non-hospitalized adults who are infected with RSV and are at high risk of severe illness.

Endpoint: Mean number of days alive and free from hospital stay (hospital-free days) through Day 28.

Treatment condition: the randomized treatment (sisunatovir or placebo).

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death directly into the endpoint.

Population-level summary: difference in means between treatments.

Estimands for the other secondary outcome measures that are considered supportive of the primary and key secondary outcome measures will be provided in the statistical analysis plan.

9.1.2. Multiplicity Adjustment

Following the positive test of the primary endpoint, sequential testing will be performed for the key secondary endpoints in the following order:

- Proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28.
- Proportion of participants with progression of LRTI through Day 10.
- Proportion of participants with development of LRTI through Day 10.
- Proportion of participants with resolution of LRTI at Day 15.
- Mean number of days alive and free from hospital stay (hospital-free days) through Day 28.

A key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant, ie, p-value ≤ the applicable alpha level.

The key secondary endpoints will not be tested at the second efficacy IA but will be tested according to the following framework [22] (see Section 9.4 for more details):

- If the study is stopped early for efficacy at the second efficacy IA, the key secondary endpoints will be tested on the accrued set of all participants available after enrollment has been stopped and all randomized participants have completed the study.

- If the study is not stopped early for efficacy at the second efficacy IA, the key secondary endpoints will be tested at the conclusion of the full study, if the test for the primary endpoint is statistically significant at that final analysis.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant, or their legally authorized representative, agreed to participate in this clinical study following completion of the informed consent process and the participant was randomized to study intervention.
Full analysis set (FAS)	All participants randomly assigned to study intervention.
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 study intervention they received.
PK concentration population	All participants who received at least 1 dose of sisunatovir and in whom at least 1 concentration value can be reported.
PK parameter analysis population	All participants who received at least 1 dose of sisunatovir and in whom at least 1 of the PK parameters of interest can be reported.

Defined Analysis Set	Description
Modified Intent-to-Treat - Infected (mITT-infected)	All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and who have confirmed RSV infection at randomization that is defined as detectable RSV RNA levels by RT-PCR as measured by the central laboratory. Participants will be

Defined Analysis Set	Description
	analyzed according to the study intervention to which they were randomized.

For the primary efficacy analysis and analyses of the key secondary endpoints, the mITT-infected set will be used. The Safety Analysis Set will be used in the analyses of the safety data.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses, including 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

Descriptive statistics for all efficacy endpoints by treatment group and visit (as applicable) will be provided.

The number of participants screened, randomized to the double blind treatment phase, completing the study drug administration, and completing the study will be summarized from the FAS. The reason for all discontinuations will be summarized by treatment group.

Baseline demographic and other characteristics will be tabulated for the FAS and summarized by treatment group. Quantitative variables will be described by standard descriptive statistics (mean, standard deviation, minimum, and maximum), and qualitative variables will be summarized by frequency tables with number and proportion in each category (with the corresponding sample sizes).

For continuous endpoints, a mixed model repeated measures (MMRM) analysis of covariance will be used to analyze change from baseline over time. Estimated mean differences between treatments and their respective 95% CI and p-values will be calculated.

For binary endpoints, proportions of participants with the event will be summarized for each group. Treatment comparisons between the groups will be presented as the difference of proportions with its 95% confidence interval using a similar analysis method as the primary endpoint.

For categorical endpoints, proportions of participants for each category will be summarized for each group.

For count endpoints, the total number of the events and average number of events will be summarized for each group.

Imputation of missing data within efficacy variables and endpoints will be computed according to the rules specified in the SAP. Details on covariates to be included in models will also be specified in the SAP.

9.3.2. Primary Endpoint/Estimand Analysis

9.3.2.1. Definition of Endpoint

The primary endpoint is the proportion of participants with RSV-related hospitalization or death from any cause through Day 28.

For the primary endpoint, hospitalization is defined as ≥24 hours of acute care in a hospital or similar acute care facility (see Section 8.2.1). This includes specialized acute medical care unit within an assisted living facility or nursing home.

9.3.2.2. Main Analytical Approach

The primary efficacy analysis will be conducted using the mITT-infected population.

The treatment difference in proportion of participants experiencing RSV-related hospitalization or death from any cause during the first 28 days of the study will be analyzed by the MN method [23]. Multiple imputation will be used to impute endpoint event status for participants who discontinue prior to the Day 28 visit without experiencing an endpoint event [24].

The above primary analysis will also be conducted for the two planned efficacy IAs. Two-sided 95% CI (adjusted for the planned interim analyses) and associated p-value for the null hypothesis of no difference between treatment groups will be presented. Significance level for assessment of efficacy will be determined using the CCI [redacted] at the second efficacy IA and the final analysis. Significance level for assessment of futility will be determined using the CCI [redacted] approach at the first and second efficacy IAs. The overall significance level is set at 2.5% (1 sided) [25] .

9.3.2.3. Sensitivity Analyses

Additional sensitivity analyses will be described in the SAP.

9.3.2.4. Supplementary Analyses

Supplemental analyses will be performed for the primary efficacy endpoint to assess the impact of baseline RSV RNA levels by RT-PCR as measured by the central laboratory, days since symptom onset, and RSV sub-species (A/B). Another supplemental analysis will be performed using the FAS.

Additional supplemental analyses will be described in the SAP.

9.3.3. Secondary Endpoints/Estimands Analysis

Proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28

The first key secondary efficacy endpoint is the proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28. The analysis for this endpoint is similar to the analysis of the primary endpoint. For this secondary endpoint, no minimum duration of hospitalization is required. If a patient is located in an urgent care or ED at time of randomization, that initial visit would not count towards assessment of this endpoint.

Proportion of participants with progression of LRTI through Day 10

The second key secondary efficacy endpoint is the proportion of participants with progression of LRTI through Day 10. Progression of LRTI is defined as progressing from no LRTI at randomization to nsLRTI-RSV or sLRTI-RSV, or from nsLRTI-RSV at randomization to sLRTI-RSV, at any time up to and including Day 10. The analysis for this endpoint is similar to the analysis of the primary endpoint.

Proportion of participants with development of LRTI through Day 10

The third key secondary efficacy endpoint is the proportion of participants with development of LRTI through Day 10. Development of LRTI is defined as not having LRTI at randomization but having nsLRTI-RSV or sLRTI-RSV at any time up to and including Day 10. The analysis for this endpoint is similar to the analysis of the primary endpoint.

Proportion of participants with resolution of LRTI at Day 15

The fourth key secondary efficacy endpoint is the proportion of participants with resolution of LRTI at Day 15. Resolution of LRTI is defined as having nsLRTI-RSV or sLRTI-RSV at randomization and having no LRTI at Day 15. The analysis for this endpoint is similar to the analysis of the primary endpoint.

Mean number of days alive and free from hospital stay (hospital-free days) through Day 28

The fifth key secondary efficacy endpoint is the mean number of days alive and free from hospital stay (hospital-free days) through Day 28. All hospital days will be counted, regardless of whether or not the hospital admission or hospital day is related to RSV. The analysis for this endpoint will be based on a model with treatment group as a factor and symptom duration as a covariate.

- **Additional efficacy-related secondary endpoints**
    - Proportion of participants with progression of LRTI through Day 3, 5, 15, and 28.

- Proportion of participants with development of LRTI through Day 3, 5, 15, and 28.
- Proportion of participants with resolution of LRTI at Day 3, 5, 10, and 28.
- Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28.
- Number of RSV related days in hospital through Day 28.
- Number of RSV related days in ICU through Day 28.
- Proportion of participants with a clinical response of Improvement or Resolution at Day 5, 10, 15, and 28.
- Proportion of participants with undetectable RSV viral load at each study visit through Day 28.
- Change from baseline in RSV viral load at each study visit through Day 28.

Details on the definitions and analyses of secondary endpoints will be described in the SAP.

9.3.3.1. Pharmacokinetics

The plasma concentrations of sisunatovir will be listed and descriptively summarized by specific PK sampling windows or nominal sampling time as appropriate. Summary profiles (mean and median plots) of the sisunatovir plasma concentration data will be plotted using actual and nominal time or time windows, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

An iterative population PK model is being developed from Phase 1 and 2 sisunatovir studies. This model is developed with successive updates and validations from available data as studies complete. The final population PK model will be used to simulate plasma concentration-time curves for sisunatovir for individuals (if feasible) and to calculate post-hoc estimates of PK parameters (CL/F, C_{max}, C_{min}, AUC_{tau} and $t_{½}$).

Data permitting, geometric mean of PK parameters estimated from the final population PK model will be summarized. A stand-alone population PK modeling and simulation analysis plan will be prepared, and the results will be reported in a stand-alone report outside of the clinical study report.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Analysis methodology for tertiary/exploratory endpoints will be described in the SAP.

Results of tertiary/exploratory endpoint analyses will be described in the CSR to the extent possible. Due to the exploratory nature of the endpoints, the associated data analyses may not be complete at the time of CSR preparation. If results of tertiary/exploratory endpoint

analyses cannot be included in the CSR, they will be disseminated to the scientific community to the extent possible through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety population.

The safety assessments include AEs, laboratory assessments, physical examinations, and vital signs. Summaries of incidence rates of AEs (eg, treatment-emergent AEs, SAEs, discontinuations due to AEs) will be performed, as will summaries of categorical assessments of laboratory and vital signs data. No formal statistical analysis will be conducted on any of the safety data listed above.

9.3.6. Other Analyses

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

Long-term health outcomes and healthcare utilization from real world data in the United States will be collected during and after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

A planned efficacy IA for futility will be conducted and reviewed by an independent E-DMC after approximately 45% of planned participants in the mITT-infected analysis set (ie, approximately 45% of CCI participants) complete Day 28 assessments or have discontinued the study. A second planned efficacy IA for early efficacy and futility with a sample size re-assessment will be conducted and reviewed by an independent E-DMC after approximately 65% of planned participants in the mITT-infected analysis set (ie, approximately 65% of CCI participants) complete Day 28 assessments or have discontinued the study. Both the futility rules are non-binding.

At the time of planning the Phase 2/3 study, there was uncertainty about the rate of RSV-related hospitalization or death in the primary analysis population and about the treatment effect of sisunatovir. Hence, a sample size re-assessment will be conducted during the second efficacy IA based on conditional power [26]. The sample size can be adjusted one time if the conditional power falls between 30% and 90%, and the increase will be CCI A well-established method described by Cui, Hung, and Wang (1999) [27] will be used to control the Type I error probability [28].

The nominal significance level for the planned interim and final proportion of hospitalization/death analyses is determined by means of the CCI with an overall 1-sided type I error rate of 2.5%.

For the first efficacy IA (45%), a CCI approach will be used for futility decision making, with CCI indicating futility. For the second efficacy IA (65%), an CCI will be used for early efficacy decision making, ie, reject H_{0P} (null hypothesis for primary endpoint) with CCI function approach will be used for futility decision making, with CCI indicating futility. The final p-value for rejecting H_{0P} will be ≤CCI The actual stopping boundaries will depend on the exact timing of the IA. If the early efficacy boundary is crossed at the second efficacy IA, a final analysis will be conducted as a supportive analysis. If futility or early efficacy are demonstrated at either of the efficacy IAs, the E-DMC recommendations will be reviewed by the Sponsor Management Committee and a determination will be made regarding continuation or cessation of randomization into the study.

The key secondary endpoints will not be tested at the second efficacy IA, but if the early efficacy boundary is crossed for the primary endpoint at the second efficacy IA and the study is stopped, the key secondary endpoints will be tested on the final accrued data after enrollment has been stopped and all randomized participants have completed the study. Group sequential boundaries with an overall 1-sided alpha level of 0.025 and a CCI will be used [22], accounting for the planned efficacy IAs.

If the study is stopped for early efficacy at the second efficacy IA, the efficacy decision criteria for the key secondary endpoints will be based on the information fraction as per the final accrued study population. As an example, if the study is stopped early and CCI% of the originally planned number of participants are available for the analysis of key secondary endpoints, the efficacy decision making criteria would be to reject H_{0S} (null hypothesis for key secondary endpoint) with 1-sided p-value ≤CCI The final p-value for rejecting H_{0S} would have been ≤CCI (1-sided).

If the study is not stopped early for efficacy at the second efficacy IA, the key secondary endpoints will be tested at the conclusion of the full study using a Pocock alpha-spending function, if the test for the primary endpoint is statistically significant at that final analysis. The final alpha level will be determined using an information fraction for the second efficacy IA based on the amount of accumulated data that would have been used for the analysis of the key secondary endpoints if the study had been stopped early for efficacy at the second efficacy IA.

Before any IA is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an E-DMC charter. In addition, the analysis details will be documented and approved in the SAP. To maintain the blind while the study is ongoing, the results of the IAs will be publicly disclosed together with the results of the primary and secondary analyses within 1 year after the end of the study.

In addition to the planned efficacy IA 1 and IA 2, an IA will be performed to evaluate PK, ie, confirm sisunatovir exposure in adult RSV participants. The PK IA will be conducted when CCI participants randomized (approximately CCI in the PK concentration

population) have completed the CCI PK assessments. No efficacy or safety data will be analyzed at this interim time point. Study enrollment will likely be ongoing at the time of the PK IA. Blinding to treatment assignment will be maintained at all investigational sites. Results of the PK IA will not be shared with the investigators prior to completion of the study. Participant-level unblinding will be restricted to a small unblinded team performing the PK IA, who will be independent from the study and have no other responsibilities associated with the study. Study monitors will remain blinded. When the PK IA is performed, an internal, independent, unblinded review committee separate from the study team will review population PK model-derived plasma concentration-time curves and PK parameters for sisunatovir including steady-state trough concentrations. No safety or efficacy data will be used to inform the PK IA.

9.5. Sample Size Determination

Due to scarcity of contemporary published literature, sample size calculations were based on estimates from real-world databases in the United States. Among adults who were diagnosed with RSV in an outpatient setting, the proportion with hospitalization by day 28 observed across real-world databases ranged from CCI% to CCI% for adult patients with CCI years, heart failure, chronic obstructive pulmonary disease, or asthma [internal data on file]. Therefore, an event rate of CCI% was assumed for the placebo group for this study.

This study is designed to have 90% statistical power to show a difference between the treatment arms (sisunatovir versus placebo) of CCI% in the proportion of participants hospitalized/dying, using a 1-sided Type I error rate of 2.5%. The proportion of hospitalization/death in the placebo arm is assumed to be CCI%. A CCI% absolute difference represents a CCI% relative reduction from placebo.

Using East 6.5 for a 2-sample proportion test with the planned efficacy IAs (see Section 9.4), the sample size needed to detect this difference with 90% power at a 1-sided significance level of 2.5% was determined to be CCI randomized participants.

Assuming a CCI the required total sample size for the primary analysis will be increased to approximately CCI participants. Assuming CCI as measured by the central laboratory, and thus will not be included in the primary analysis, the planned total number of participants to be randomized will be increased to approximately 2375. However, study enrollment will be stopped after approximately CCI participants are available for the primary analysis.

Enrollment of participants CCI at randomization will be limited to approximately CCI%. Enrollment of participants ≥65 years of age with none of the other risk factors will be limited to approximately CCI%.

A sample size re-assessment will take place during the second efficacy IA with potential for an CCI

Additionally, for the key secondary endpoint of progression to LRTI through Day 10, it is

anticipated that at least [redacted]% of participants will have no LRTI or only nsLRTI-RSV at randomization, and thus be included in this analysis. Assuming [redacted]% of placebo participants will experience progression, and that sisunatovir will provide a [redacted]% relative reduction from placebo in the event rate, marginal power after stopping due to early efficacy or proceeding to full study conclusion is expected to be at least 90%.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

Vulnerable participants, such as elderly individuals with impaired cognitive function, may be enrolled, with the consent process being completed by their legally authorized representative, if the expected benefits of receiving sisunatovir outweigh the risks of trial participation, in the opinion of the investigator.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) 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 or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative.

The participant or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative (if allowed by local regulations).

10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will

maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

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

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

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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

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

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

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

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor. Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

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

10.1.9. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records, for instance follow up of SAE may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

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

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

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

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

10.1.10. Study and Site Start and Closure

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

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

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

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

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

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

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

10.1.11. Publication Policy

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

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary

completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the supporting study documentation/study portal.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values; for example: calculation of estimated kidney function. 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 6. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Other
Hemoglobin	Urea	At screening:
Hematocrit	Creatinine	FSH[b]
RBC count	Cystatin C[a] (at Screening or Baseline)	Pregnancy test (β-hCG)[c]
Platelet count	Sodium	
WBC count	Potassium	
Total neutrophils (Abs)	AST, ALT	
Eosinophils (Abs)	GGT	
Monocytes (Abs)	Total bilirubin	
Basophils (Abs)	Alkaline phosphatase	
Lymphocytes (Abs)	Albumin	
	Total protein	
	Fasting glucose	

a. Cystatin C (Scys): Screening or Baseline Scys may help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1).
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC.

Table 7. Protocol-Required Laboratory Assessments – Reflex Testing

Hematology	Chemistry
If Hb/RBC abnormal: MCV, MCH, MCHC Neutrophils (%) Eosinophils (%) Basophils (%) Lymphocytes (%) Monocytes (%) RBC morphology RBC distribution width	Required: For suspected DILI: AST/ALT T bili, albumin, CK, direct and indirect bili, GGT, PT/INR, eosinophils (%), alkaline phosphatase. The following additional testing may be warranted: Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) Total bile acids Liver imaging For suspected DICI/DIKI: Creatinine (Screat) Cystatin C[a] (Scys) eGFR (Screat only and combined Screat+Scys)[b] Urine albumin-to-creatinine-ratio (UACR)

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1).
b. Screening and Baseline eGFR is measured with creatinine (Screat)-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess presence or absence of post-baseline change in kidney function.

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/analyte 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.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

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

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

AE and SAE Recording/Reporting
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs using the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2)

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

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

Safety Event	**Recorded on the CRF**	**Reported on the** CT SAE Report Form **to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All All nonserious AEs leading to discontinuation of study intervention	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB All nonserious AEs leading to permanent discontinuation or 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)* Notification of EDP alone (not associated with an AE or SAE) is not required when the study population is pregnant women. However, if the mother or the fetus experiences any SAE, the information is reported to Pfizer Safety 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 nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories, which are based on the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) [21]:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	POTENTIALLY LIFE-THREATENING event
5	DEATH RELATED TO adverse event

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Transmission of the CT SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

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

    OR

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

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

10.4.3. Woman of Childbearing Potential

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

If fertility is unclear (eg, amenorrhea 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. Premenarchal.

2. 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.

3. 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 of age and not using hormonal contraception or HRT.
    - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

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

    - Oral + barrier*
    - Injectable + barrier*

8. Sexual abstinence

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

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

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

10.5. Appendix 5: 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 Research samples will be stored indefinitely or for another period as per local requirements.

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. 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]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated.

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Table in Section 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).

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 [30]

eGFR (mL/min/1.73m²)

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

10.7.3. 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
    - 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) will be according to KDIGO criteria for adult participants.

KDIGO criteria grade (G)	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15

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

KDIGO albuminuria (A) criteria	A1	A2	A3
	<3 mg/mmol	3 to 30 mg/mmol	>30 mg/mmol

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-second duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as SAEs

- QTcF prolongation >500 ms.
- Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex >120 ms).
- New-onset right bundle branch block (QRS complex >120 ms).
- Symptomatic bradycardia.
- Asystole
  - In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;

- In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.

- Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

- Type II second-degree (Mobitz II) AV block.

- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.

- Sustained ventricular tachyarrhythmias (>30-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 should not be taken with sisunatovir for the period of time at least equal to the required washout period listed in the table, and throughout the dosing part of the study. Administration of CCI must have ended 5 days prior to randomization and administration of CCI must have ended at least 12 hours prior to randomization. The use of CCI is allowed with CCI study drug administration). Any administration of CCI is prohibited during treatment with sisunatovir.

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

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs) if the overall benefit:risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

- CCI must not be taken from at least 14 days prior to randomization and during treatment with sisunatovir.
- CCI must not be taken from at least 14 days prior to randomization (21 days for CCI and during treatment with sisunatovir.
- CCI must not be taken from at least 5 days prior to randomization and during treatment with sisunatovir.
- Sisunatovir also may be an inhibitor of CCI and CCI therefore, CCI may be administered with caution during treatment period.

Sisunatovir is a CCI and therefore medications that are sensitive CCI substrates CCI will be permitted provided that the participants are appropriately monitored by the investigator who should be aware that the active investigational product (sisunatovir) may compete for the metabolism of such products, resulting in higher drug levels of these medications.

Prohibited concomitant medication list

This is not an all-inclusive list. If a medication is not listed, it should not automatically be assumed it is safe to co-administer. Appropriately qualified site staff will review all

concomitant medications to determine if they are prohibited. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

For medications that fall in multiple categories, the most stringent restriction applies.

CCI		**Required Washout Period**
		Prohibited 14 days prior to randomization through the end of the treatment period
		Prohibited 14 days (21 days for CCI prior to randomization through the end of the treatment period
		Prohibited 5 days prior to randomization through the end of the treatment period

CCI		Required Washout Period
		Prohibited 5 days prior to randomization through the end of the treatment period
		Prohibited during the treatment period through 5 days after last dose of study medication.
		Prohibited 5 days prior to randomization through the end of the treatment period
		Prohibited 12 hours prior to randomization through the end of the treatment period.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use or needs to be administered with caution or dose adjusted.

Medications that interact with sisunatovir that may be used with caution or where a dose adjustment may be required

CCI		
		Use with caution or dose adjustment required (consult the product label for more information)
		Use with caution or dose adjustment required (consult the product label for more information)
		Use with caution or dose adjustment required (consult the product label for more information)

10.10. Appendix 10: Country-Specific Requirements

10.10.1. United States

Participants in the United States will be invited to participate in optional, additional research using real world data to describe long-term health outcomes and healthcare utilization for 12 months after taking the study medicine. Real world data may consist of large commercially available databases of medical claims, billing data, pharmacy claims, and electronic health records. Long-term follow-up will be conducted by accessing and evaluating real-world data sources using a technology called Tokenization.

Study participants who consent to participate in additional research using real world data via tokenization will have a unique identifier generated (ie, token) through a third-party vendor.

Tokenization transforms patient identifiable information (first name, last name, sex at birth, date of birth and zip code) into an irreversible random string of characters that can be used to securely link patient-level data from the clinical study database (eg, treatment group assignment of sisunatovir or placebo) with real world data sources (eg, medical visits observed in insurance claims) to evaluate medical outcomes (eg, number and type of medical visits and survival) that occur after the main study ends.

Specific instructions for sites regarding how to record data on a secure website to enable token generation can be found in site training materials.

10.10.1.1. Management and reporting of adverse events/adverse reactions for additional research using real world data

This additional research involves a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Therefore, investigators and real world data vendors do not have any AE reporting requirements related to any medical information obtained as part of additional research using real world data (secondary data).

10.10.2. China

Retained research samples in Section 8.6.2 and Section 8.7.5 will not be collected in China. Biological samples leftover after analysis will be destroyed at a designated center in China.

10.10.3. United Kingdom

WOCBP enrolled in the United Kingdom will undergo a serum or whole blood pregnancy test at the screening visit to confirm negative pregnancy prior to first dose. A urine pregnancy test will be used for screening in other countries.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
%CV	percent coefficient of variation
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ACR	albumin-to-creatinine ratio
AE	adverse event
AKI	acute kidney injury
CCI [redacted]	
ALT	alanine aminotransferase
ARI	acute respiratory infection
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{12}	area under the concentration-time curve from time zero to 12 hours
CCI [redacted]	
AUC_{inf}	area under the serum concentration-time profile from time zero extrapolated to infinite time
AUC_{tau}	area under plasma concentration time curve over dosing interval
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
CCI [redacted]	
BP	blood pressure
bpm	beats per minute
CAR-T	chimeric antigen receptor T-cell
CD	cluster of differentiation
CF	cystic fibrosis
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	clearance
CL/F	oral clearance
C_{max}	maximum observed concentration
C_{min}	minimum concentration
$C_{troughSS}$	trough (pre-dose) concentration at steady state
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019

Abbreviation	Term
CPAP	continuous positive airway pressure
C-QT	concentration QT analysis
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CT	computed tomography/clinical trial
CTIS	Clinical Trial Information System
CV	challenge virus
CCI [redacted]	
DAIDS	Division of Acquired Immunodeficiency Syndrome
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DPB	dry powder blend
DU	dispensable unit
EC	ethics committee; exclusion criterion
EC_{90}	90% maximal effective concentration
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ED	emergency department
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
EQ-5D-5L	a standardized, validated, generic health related quality of life questionnaire used in clinical and economic HTA evaluations expanded to a 5 level scale
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAS	full analysis set
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
CCI [redacted]	

Abbreviation	Term
GGT	gamma-glutamyl transferase
GI	gastrointestinal
H2	histamine 2 receptor
H_{0P}	null hypothesis for primary endpoint
H_{0S}	null hypothesis for key secondary endpoint
Hb	hemoglobin
HCP	health care professional
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HTA	health technology assessment
IA	interim analysis
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRT	Interactive Response Technology
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney disease outcomes quality initiative
LBBB	left bundle branch block
LFT	liver function test
LRTI	lower respiratory tract infection
MAD	multiple ascending dose
CCI [redacted]	
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mITT	modified intent to treat
MMRM	mixed model repeated measures
MN	Miettinen-Nurminen
MQI	medically qualified individual
CCI [redacted]	
NA	not applicable
NIMP	noninvestigational medicinal product

Abbreviation	Term
NOAEL	no observed adverse effect level
NP	nasopharyngeal
nsLRTI-RSV	RSV-related non-severe lower respiratory tract infection
NTI	narrow therapeutic index
NYHA	New York Heart Association
CCI	[redacted]
PAH	pulmonary arterial hypertension
PCR	polymerase chain reaction
PF	pulmonary fibrosis
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	Oral(ly)
PR	pulse rate
PRO	patient reported outcome
PSSA	Pfizer's Serious AE Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
q12h	every 12 hours
QSP	Quantitative Systems Pharmacology
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
RBC	red blood cell
R_{ac}	accumulation ratio based on AUC (observed)
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase PCR
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Screat	serum creatinine
Scys	serum cystatin C
sLRTI-RSV	RSV-related severe lower respiratory tract infection
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	half life
T bili	total bilirubin
TEAE	treatment emergent adverse event
Tmax	time taken for drug to reach Cmax after administration

Abbreviation	Term
TNF	tumor necrosis factor
UACR	urine albumin/creatinine ratio
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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