Title Page

AN INTERVENTIONAL, PHASE 1b, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, MULTI-CENTER, DOSE-FINDING STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SISUNATOVIR IN PEDIATRIC PARTICIPANTS UP TO AGE 60 MONTHS WITH RESPIRATORY SYNCYTIAL VIRUS (RSV) LOWER RESPIRATORY TRACT INFECTION (LRTI)

Study Intervention Number:	PF-07923568
Study Intervention Name:	Sisunatovir
US IND Number:	143479
EU CT Number:	2023-504425-39-00
ClinicalTrials.gov ID:	NCT06102174
Pediatric Investigational Plan Number:	PIP: EMEA-002529-PIP01-18
Protocol Number:	C5241009
Phase:	Phase 1b
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A Study to Learn About the Safety, Tolerability and Blood Levels of Study Medicine (called sisunatovir) in Infants and Children with RSV Lower Respiratory Tract Infection

Document History

Document	Version Date
Amendment 4	11 March 2024
Amendment 3	27 January 2024
Amendment 2	13 September 2023
Amendment 1	26 June 2023
Original protocol	14 April 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 4 (11 March 2024)

Overall Rationale for the Amendment: The primary purpose of this amendment is to address the new medication restrictions on acid reducing agents (eg, PPI, H2 blockers and antacids) based on preliminary results from a DDI study (C5241017), incorporate protocol clarifications, and corrections to identified errors.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Added additional bullet point to exclusion criterion #16 – "Has taken within 5 days before dosing or require during the dosing period of the study, any proton pump inhibitors. Has taken within 12 hours before dosing or require during the dosing period of the study, any H2 blockers."	Based on preliminary results from a DDI study (C5241017) of sisunatovir tablets in coadministration with antacids that showed reduced sisunatovir plasma exposure.	Section 5.2 Exclusion Criteria
Added the following statements to: Prohibited Prior Treatment: "Administration of proton pump inhibitors must have ended 5 days prior to randomization" and "Administration of H2 blockers must have ended at least 12 hours prior to randomization." Prohibited During the [redacted] Day Study Drug Administration: "Any administration of proton pump inhibitors and H2 blockers is prohibited. The use of antacids	Based on preliminary results from a DDI study (C5241017) of sisunatovir tablets in coadministration with antacids that showed significantly reduced sisunatovir plasma exposure.	Section 6.9 Prior and Concomitant Therapy

Description of Change	Brief Rationale	Section # and Name
(such as calcium carbonate or magnesium hydroxide) is allowed with staggered dosing (ie, not within 3 hours before or after study drug administration."		
Added list of proton pump inhibitors and H2 blockers drugs to the prohibited concomitant medication table.	Based on preliminary results from a DDI study (C5241017) of sisunatovir tablets in coadministration with antacids that showed significantly reduced sisunatovir plasma exposure.	Appendix 8 Prohibited Concomitant Medications That May Result in DDI
Added the statements below to exclusion criterion 11 in Section 1.1 and exclusion criterion 12 in Section 5.2: First bullet point – "or expected to receive equivalent dose during study drug treatment." Second bullet point – "or expected to receive treatment with these therapeutics during study drug treatment."	To provide additional protocol clarification.	Section 1.1 Synopsis and Section 5.2 Exclusion Criteria
Removed pre-dose PK sample collection on Day [redacted] updated notes for PK blood sample in both Table 2 and Table 3, and updated Table 3 header.	To reduce number of blood draws for PK samples required from 4 to 3, and to limit blood volume collected in the study.	Section 1.3.1, Table 2 SoA, and Section 1.3.2, Table 3 Multiple Dose PK Days (For all Cohorts)
Non-Substantial Modifications		
Updated ClinicalTrials.gov ID to NCT06102174	To provide the available information.	Title page and Section 1.1 Synopsis
Removed UA collection at Days [redacted] and [redacted]	C5241003 study collected urine samples and provided reassuring safety data. UA will still be collected at baseline and is one of the reflex tests (Table 8) to be done should there be concern for potential AKI.	Section 1.3.1 SoA
Removed [redacted] Services on Day [redacted]	To provide protocol clarification that [redacted] services will only be available at Day [redacted] visit and onwards.	Section 1.3.1 SoA
The frequency of collection of social factors was reduced to Screening, Day [redacted] Day [redacted] and ET visit, and Body Weight assessment was reduced to Screening, Day [redacted] and ET visit only.	To simplify the number of assessments timepoints. The data entry for social factors is repetitive and cumulative data will be captured at the Day [redacted] and Day [redacted] visits. Repeated weight entries do not impact dosing, as dosing is determined based on baseline weight.	Section 1.3.1 SoA
Removed Record RSV related Medical Visits on Days 2 and 3.	To simplify study procedures	Section 1.3.1 SoA

Description of Change	Brief Rationale	Section # and Name
Reduced collection of SpO_2 to once daily for hospitalized participants.	To be consistent with RSV signs/symptoms collection which is only once daily.	
Added to the notes for Study Kit dispensed from IRT and parent(s)/legal guardian instructed on its use – "If parent or legal guardian is allowed to administer study drug while hospitalized, per local regulations, training should occur prior to parent or legal guardian study drug administration."	To provide additional protocol clarification.	Section 1.3.1 SoA
Deleted Table 4 Completed Sisunatovir clinical studies and Table 5 Overview of ongoing clinical studies and inserted bullet points summarizing the 7 ongoing Sisunatovir clinical studies. Changed the statement – "The thorough QT study (C5241015) demonstrated that the concentration response analyses between sisunatovir exposure (which cover a concentration range up to approximately 1.2-fold the high clinical exposure and 3.5-fold the projected therapeutic mean Cmax concentration studied in Phase 1/2 studies), the ΔΔQTcF, and HR did not identify signal of potential clinical concern (PMAR-EQDD-C524b-Pre-Poc-1664)" To: "The concentration response analyses did not identify a QT prolongation signal of potential clinical concern (PMAR-EQDD-C524b-Pre-Poc-1664)."	To simplify the protocol and reference IB (version 3, 01 March 2024).	Section 2.2.4 Clinical Overview
Added – (not counting the 12 participants from the palatability study who did not swallow sisunatovir). Updated the statement – "The most commonly reported treatment related TEAEs in adults were in the GI disorders System Organ Class: nausea, diarrhea, and abdominal pain" To: "The most commonly reported all causality treatment related TEAEs (≥10 participants) in the	To align with the updated IB (version 3, 01 March 2024).	Section 2.2.4 Clinical Overview

Description of Change	Brief Rationale	Section # and Name
multiple dose studies with sisunatovir in adults were: diarrhea, nausea, abdominal pain, and headache." Added: The preliminary results from a DDI study of sisunatovir tablets (adult formulation) in coadministration with an acid reducing agent showed a significantly reduced plasma exposure (C5241017). These new findings do not represent a safety concern; however, the reduced plasma exposure may have a potential impact on the efficacy of sisunatovir tablets.		
Added - "If the study participant is hospitalized at the time of enrolment and it is identified that they (he/she) could not attend the Day [redacted] and/or Day [redacted] visits if discharged, the investigator may at their (his/her) discretion, if local regulations allow and CCI services are not available, keep the participant in the hospital for convenience to ensure Day [redacted] and/or Day [redacted] assessments can be conducted in compliance with protocol requirements."	To allow sites flexibility to conduct Day [redacted] and/or Day [redacted] visits in order to conduct study assessments, at investigator discretion, if local regulations allow and if CCI services are unavailable.	Section 6.5 Study Intervention Compliance
Updated header from "Prohibited During the Study" to "Prohibited During the [redacted] Day Study Drug Administration."	To remove duplication and improve clarity.	Section 6.9 Prior and Concomitant Therapy
Deleted - Corticosteroids equivalent to prednisone ≥2 mg/kg daily initiated for at least 14 consecutive days within 30 days prior to study start and during study drug administration.	Not applicable. Participants would have been excluded at screening.	Section 6.9 Prior and Concomitant Therapy
Added – "for respiratory tract infection" to Antiviral and deleted – "during the dosing period of the study" and "during study treatment period" from some of the listed washout period of the prohibited medications.	To provide additional protocol clarification.	Section 6.9 Prior and Concomitant Therapy
Deleted "3.6 mL for CCI [redacted]" so that total blood sampling volume will be approximately 3.9 mL for all cohorts. Updated total volume of blood drawn from 4.6 mL to 3.9 mL.	To align with the updates made in Sections 1.3.2. and 10.2.	Section 8.1 Administrative & Baseline Procedures Section 8.3.4 Clinical Safety Laboratory Assessments.

Description of Change	Brief Rationale	Section # and Name
Removed – Glucose (random) from Table 10 and Lactate dehydrogenase (LDH). Added LDH to DILI assessment tests.	To reduce blood draw volume required in the study. If there is concern for hepatic injury, LDH is now included in list of laboratory assessments to be conducted.	Section 10.2, Appendix 2 Clinical Laboratory Tests
Updated the footnoting on Table 8	Protocol clarification and consistency.	Section 10.2, Appendix 2 Clinical Laboratory Tests
Added – "Additionally, administration of proton pump inhibitors must have ended 5 days prior to randomization and administration of H2 blockers must have ended at least 12 hours prior to randomization. The use of antacids is allowed with staggered dosing (ie, not within 3 hours of study drug administration). Any administration of proton pump inhibitors or H2 blockers is prohibited during treatment with sisunatovir."	Based on preliminary results from a DDI study (C5241017) of sisunatovir tablets in coadministration with antacids that showed significantly reduced sisunatovir plasma exposure.	Section 10.8 Appendix 8 Prohibited Concomitant Medications That May Result in DDI
Updated – "For the procedures below, the following chronology of events are proposed" to "For the procedures below, the following chronology of events are suggested, but can be modified based on investigator discretion and adherence to IMP dosing interval." The header was updated to remove "Proposed" and added "(Suggested)". Added in the text was "screening only" to 12 lead ECG.	To clarify that these are suggested and do not need to be followed.	Section 10.10.3. Appendix 10C Chronology of Procedures (Suggested)
Several additional minor editorial changes were made.	To improve clarity and readability and for maintaining consistency throughout the documents.	Throughout Protocol

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An interventional, Phase 1b, randomized, double-blind, sponsor-open, placebo-controlled, multi-center, dose-finding study to evaluate safety, tolerability, and pharmacokinetics of sisunatovir in pediatric participants up to age 60 months with Respiratory Syncytial Virus (RSV) Lower Respiratory Tract Infection (LRTI).

Brief Title:

A Study to Learn About the Safety, Tolerability and Blood Levels of a Study Medicine (called sisunatovir) in Infants and Children with RSV Lower Respiratory Tract Infection.

Regulatory Agency Identification Number(s):

US IND Number:	143479
EU CT Number:	2023-504425-39-00
ClinicalTrials.gov ID:	NCT06102174
Pediatric Investigational Plan Number:	PIP: EMEA-002529-PIP01-18
Protocol Number:	C5241009
Phase:	Phase 1b

Rationale:

The purpose of this study is to establish safety, tolerability, pharmacokinetic (PK) and guidance for dosing of sisunatovir in a pediatric population (1 day to 60 months of age) with RSV-LRTI, for further clinical development of sisunatovir. Palatability assessments will also be conducted to aid in the development of pediatric formulations of sisunatovir.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To evaluate the safety and tolerability of sisunatovir compared to placebo in participants with RSV-LRTI.	• Incidence of TEAEs. • Incidence of AEs and SAEs leading to discontinuations. • Incidence of clinically significant abnormal laboratory values and vital signs.	• Not applicable

Objectives	Endpoints	Estimands
Secondary:	**Secondary:**	**Secondary:**
• To characterize the PK of sisunatovir in participants with RSV-LRTI.	• Plasma concentrations of sisunatovir at steady state (Day CCI or later).	• Not applicable

Abbreviations: AE(s) = adverse event(s); LRTI = lower respiratory tract infection; PK = pharmacokinetic(s); RSV = respiratory syncytial virus; SAE(s) = serious adverse event(s); TEAE = treatment emergent adverse event;

Overall Design:

This study is a randomized, double-blind, sponsor-open, placebo-controlled, multicenter study in RSV-infected outpatient and hospitalized neonates, infants, and children, 1 day up to 60 months of age with RSV-LRTI. This is a dose finding study to evaluate the PK, safety, and tolerability of sisunatovir.

CCI

- Cohorts 1 and 2:
  - A: CCI
  - B:
  - C:
  - D:
- Cohort 3:
  - E: CCI
  - F:
  - B:
  - D

Although neonates are defined by the World Health Organization (WHO) as 0-27 days old, CCI

Sisunatovir or placebo will be administered every CCI (CCI in a CCI ratio, for a period of CCI for all cohorts. Sisunatovir doses expected to produce systemic steady-state exposures comparable to the CCI adult dose will be evaluated in dosing Cohort 1.

Based on analysis of PK and safety data from Cohort 1, optional Cohort 2 (2A, 2B, 2C, 2D) may be used for further dose refinement to more closely match the CCI in adults or to gather additional data on doses used in Cohort 1. Only CCI will be enrolled CCI in CCI The optional Cohort 3 (3E, 3F, 3B, 3D) may be used if additional exposure, safety, or tolerability data for a given dose in one or more of the CCI

[redacted] is needed. The [redacted] in Cohort 3 focus on those ages most susceptible [redacted] (less than [redacted]). Each cohort will enroll [redacted] participants in each dose group ([redacted] active: [redacted] placebo). In case of recruitment challenges for any cohort in the study, a minimum of [redacted] participants will be enrolled ([redacted] active: [redacted] placebo).

The Sponsor will make the final decision of doses for the cohorts, including recommendation to repeat a dose or opening enrollment of the subsequent cohort. An independent external data monitoring committee (E-DMC) will review the unblinded safety and concentration data after completion of Day [redacted] visit for each cohort (approximately [redacted] participants, [redacted] participants if there are recruitment challenges) to ensure the safety of participants. The E-DMC approval of the Sponsor's recommendation will be independently assessed for each of the different age groups and will be based on the safety/tolerability and concentration data (ie, cohorts [redacted]). If Sponsor recommends repeating the dose, an additional [redacted] participants receiving active drug and [redacted] placebo may be enrolled in the same age group within the same cohort.

Participants may be replaced at Sponsor discretion for the following reasons: if the participant's parent(s)/legal guardian withdraws consent, if the participant misses any dose before providing the [redacted] sample on Day [redacted] or [redacted] if the participant misses any PK samples, if the IMP is discontinued, if the participant's RSV test result at screening are not confirmed by the central laboratory RSV test result, if participant was exposed to a prohibited concomitant medication or if Day 1 RSV RNA level by RT-qPCR is less than the lower limit of quantification.

Number of Participants:

Approximately a maximum of 108 evaluable participants [redacted] in each cohort + [redacted] additional in each cohort if necessary) and minimum of approximately [redacted] evaluable participants will be enrolled (based on a minimum of [redacted] participants per cohort) and receive study intervention.

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

Study Population:

Key inclusion and exclusion criteria are listed below.

Inclusion Criteria

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

1. Participants 1 day to ≤60 months of age and weight ≥2.5 kg to ≤23 kg.

2. A positive RSV diagnostic test with result available in source document to confirm eligibility either according to routine site practice or Investigator sites may use RSV point-of-care (POC) test kits that are provided for this study. RSV diagnostic test, antigen or molecular test is acceptable, and should be collected within [CCI] hours of randomization.

3. Evidence of LRTI by the presence of ≥1 from any of the following 4 categories (a through d):

   a. Increased respiratory rate for age:
      - <2 months: ≥60 bpm
      - ≥2 to <12 months: ≥50 bpm
      - ≥12 to ≤60 months: ≥40 bpm
   b. SpO_2 < 95% on room air
   c. Increased respiratory effort as evidenced by ≥1 of the following:
      - Grunting with expiration
      - Nasal flaring
      - Retractions
   d. One or more of the following exam findings on auscultation:
      - Wheezing
      - Rhonchi
      - Rales or crackles

4. RSV-related signs and/or symptoms must be present for ≤[CCI] days at time of randomization.

Exclusion Criteria

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

1. Premature infants (gestational age less than 35 weeks) AND <1 year of post-natal age. Note: Infants 35- and 36- week gestational age are permitted if they weigh at least 2.5 kg and are at least 2 months post-natal age.

2. CCI with intrauterine growth restriction defined by having 3 or more of the following:

    - Birth weight <10th percentile on population-based or customized growth charts
    - Head circumference <10th percentile
    - Length <10th percentile
    - Prenatal diagnosis of fetal growth restriction
    - Maternal pregnancy information associated with fetal growth restriction (eg, maternal hypertension, pre-eclampsia)

3. Any clinically significant electrocardiogram (ECG) abnormality in a participant's medical history, or in the pre-dose ECG that per investigator judgement may affect participant safety or interpretation of study results. Note: If sinus tachycardia is present, and not worse than expected due to the underlying disease, participant may be considered at investigator discretion, if the sinus tachycardia is not expected to interfere with evaluation of response to study intervention.

4. Known history of hepatic disease, concern for active acute or chronic viral hepatitis, or acute hepatic failure.

5. Participants >CCI days only: Known history of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or T bili abnormalities >2 × upper limit of normal (ULN) within 6 months of screening. Laboratory assessments not required at screening for participants >CCI days unless deemed necessary by the investigator to confirm normal hepatic function. **Note:** Participants with history of elevated bilirubin due to neonatal hyperbilirubinemia that is resolved, with T Bili values within reference range, may be enrolled.

6. History of epilepsy or seizures. Participants with a history of febrile seizures will be permitted to enroll.

7. Expected to receive or has received an antiviral for another respiratory viral infection (eg, influenza or COVID-19) within 10 days of screening.

8. Suspected or confirmed clinically significant moderate or severe bacterial infection (eg, bacterial pneumonia, bacteremia), that may interfere with the evaluation of response to the study intervention, at investigator discretion. Participants with mild, localized infections such as otitis media or urinary tract infection (UTI) can be included.

9. Evidence of severe respiratory failure requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). **Note**: Participants requiring non-invasive ventilation, including high flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP), remain eligible for the study.

10. Known to have significant comorbidities, including genetic disorders (eg, trisomy 21); cardiopulmonary diseases (eg, hemodynamically significant congenital heart disease);

significant pulmonary disease (eg, cystic fibrosis); history of surgery for diaphragmatic hernia; any hereditary or acquired metabolic diseases, hematological or other malignancy; or is known to be HIV positive; has evidence of severe neurologic impairment or developmental delay that would limit the ability to administer investigational medicinal product (IMP) or evaluate the safety or clinical response to IMP. **Note:** Preterm participants (if <35 weeks gestational age must be at least one year post-natal age) with bronchopulmonary dysplasia (chronic lung disease of prematurity) remain eligible for enrollment.

11. Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications.

    - Has received corticosteroids equivalent to prednisone ≥2 mg/kg daily for at least 14 consecutive days within 30 days prior to study start or expected to receive equivalent dose during study drug treatment. Inhaled/nebulized or topical (skin, eyes, or ears) corticosteroids are permitted, except those prohibited.

    - Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study start or expected to receive treatment with these therapeutics during study drug treatment.

12. Any medical, developmental, or behavioral condition (including history of self-harmful behaviors) or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
13. Malformation of the gastrointestinal tract including unresolved pyloric stenosis, history of necrotizing enterocolitis, short bowel, or other significant condition that would alter drug absorption or increase the risk of diarrhea.
14. Has significant oral and/or maxillofacial malformations that would limit the ability to administer IMP.
15. Baseline 12-lead ECG with QTcF ≥450 ms.

Study Arms and Duration:

Total duration of study participation for each participant is ~ 5 weeks (Screening 1-2 days; Treatment period is [redacted] days (2 doses daily Day 1 to Day 5) or 6 days (if only 1 dose received on Day 1) for a total of [redacted] doses; Follow-up period is [redacted]

CCI). If the participant receives only one dose on day 1, dosing will continue until Day 6, to complete the CCI doses.

Study Intervention(s)		
Intervention Name	**PF-07923568 (sisunatovir)**	**Placebo for PF-07923568 (sisunatovir)**
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	CCI capsule dispersed in CCI for oral ROA or nasogastric tube ROA	Matching Experimental dispersed in CCI for oral ROA or nasogastric tube ROA
Unit Dose Strength(s)	CCI mg/mL (50 mg sisunatovir CCI into CCI CCI	Matching Experimental
Route of Administration	Oral or nasogastric tube	Oral or nasogastric tube
Study Arm(s)		
Arm Title	Sisunatovir	Placebo
Arm Description	Participants will receive CCI doses of sisunatovir, CCI	Participants will receive CCI doses of placebo, CCI

Statistical Methods:

A sufficient number of participants will be screened to achieve approximately CCI evaluable participants randomized to study intervention across cohorts. The number randomized may be increased if Sponsor recommends repeating a dose, ie, an additional CCI active and CCI placebo may be enrolled in the same cohort. This totals to approximately a maximum of 108 evaluable participants (CCI in each cohort + CCI additional in each cohort if necessary) to be enrolled and receive study intervention. The sample size is empirically selected and is not based on statistical power calculation. The minimum number of participants (based on a minimum of CCI participants per Cohort) is approximately CCI evaluable participants as Cohorts 2 (2A, 2B, 2C, 2D) and 3 (3E, 3F, 3B, 3D) are optional in the study.

Safety Analysis:

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study

intervention. Participants will be analyzed according to the product (sisunatovir / placebo) they actually received.

AEs, blood pressure (BP), pulse rate, SpO_2, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory or vital sign abnormality of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Pharmacokinetic Analysis:

The final population PK model will be used to simulate plasma concentration-time curves for sisunatovir for individuals and to calculate post-hoc estimates of PK parameters (CL, C_{max}, C_{min}, AUC and $t_{½}$) by age group.

The plasma concentrations of sisunatovir will be listed and descriptively summarized by nominal PK sampling time, treatment, age group, and cohort. Individual participant and summary profiles (mean and median plots) of the plasma concentrations data will be plotted by treatment, age group using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Data permitting, geometric means of PK parameters estimated from the final population PK model will be summarized descriptively by treatment and age group.

Ethical Considerations:

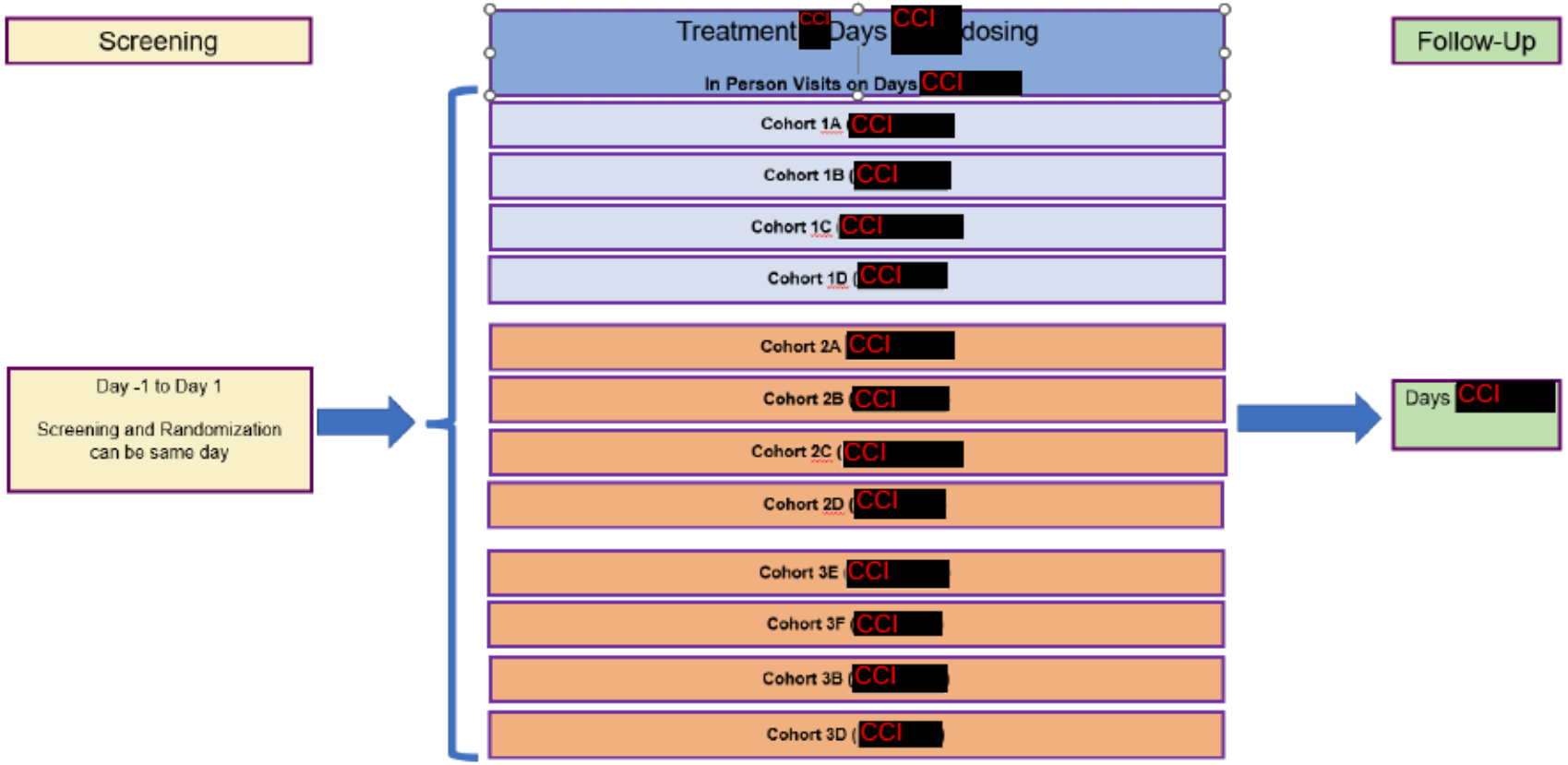
RSV is ubiquitous and is known to infect almost all children by 2 years of age. There is an unmet need for treatment of RSV infection and current management primarily consists of supportive care. The results of previous studies of sisunatovir support the investigation of sisunatovir for the treatment of RSV infection. The purpose of this double-blind, placebo-controlled study is to establish safety, tolerability, PK and guidance for dosing of sisunatovir in a pediatric population (up to 60 months) with RSV-LRTI for further clinical development of sisunatovir in the pediatric population.

The trial-specific risks and burdens for participants include the requirement for multiple visits, with one visit of extended duration, discomforts while undergoing study assessments (eg, blood draws, nasopharyngeal swabs), and the total blood volumes required. The study also includes the neonatal population with RSV-LRTI, with similar risks and burdens as described above. Based on clinical studies with sisunatovir thus far, gastrointestinal symptoms were the most commonly reported adverse events. Nonclinical studies suggested that the potential risks for sisunatovir may include cardiovascular, gastrointestinal, and hepatobiliary system effects. The doses proposed in this study provide exposures well below the PK stopping limit No Observed Adverse Effect Levels (NOAELs). Additionally, the proposed doses are targeting steady-state exposures comparable to CCI [redacted] in adults, which were found to robustly decrease viral load and alleviate RSV symptoms relative to placebo (C5241002). Taking into account the measures to minimize risk to study participants, the potential benefit to participants with RSV-LRTI and the potential risks identified in association with sisunatovir, this dose-finding study is justified by the

anticipated benefits of sisunatovir in the clinical development of sisunatovir for the pediatric population with RSV-LRTI.

There are currently no approved RSV antivirals available, and thus no active control can be proposed as comparator. The comparator for this study is participants receiving placebo. Each cohort evaluated in the study will have participants on placebo. The placebo group is required for assessing the safety, tolerability, and palatability of the study intervention. All participants (including participants receiving placebo) enrolled in the study will receive the SOC.

1.2. Schema



- Cohorts in orange are optional.
- Total N can range from CCI to approximately a maximum 108 evaluable participants.
- N=CCI CCI sisunatovir: CCI placebo) in Cohorts 1, 2 and 3 CCI (A, B, C and D in Cohorts 1 and Cohort 2; E, F, B and D in Cohort 3 CCI), minimum N of CCI CCI sisunatovir: CCI placebo).
- Age band CCI

- Cohorts 1A, 1B, 1C can run concurrently.
- Cohort CCI randomized CCI reviewed by E-DMC.
- E-DMC data review for each Cohort after Day CCI completion.
- If Sponsor recommends repeating the dose, additional CCI active and CCI placebo may be enrolled in the same cohort (limit once per cohort).
- See Table 1 below for Cohort details.

1.2.1. Cohort Details

Table 1. Cohort Details

Cohort	Age Band	Timing of Cohorts	Size*	Dose	Objective	Optional Cohort	E-DMC Concentration and Safety Review
Cohort 1							
1A	CCI	Parallel: 1A, 1B, 1C	CCI Active: Placebo);	CCI (total CCI doses) comparable to CCI)	Assess safety, PK and tolerability	No	Yes
1B		Parallel: 1A, 1B, 1C	Active: Placebo);	CCI (total CCI doses) comparable to CCI	Assess safety, PK and tolerability	No	Yes
1C		Parallel: 1A, 1B, 1C	Active: Placebo);	CCI (total CCI doses) comparable to CCI)	Assess safety, PK and tolerability	No	Yes
1D		After CCI	Active: Placebo);	CCI	Assess safety, PK	No	Yes

Table 1. Cohort Details

Cohort	Age Band	Timing of Cohorts	Size*	Dose	Objective	Optional Cohort	E-DMC Concentration and Safety Review
				CCI	and tolerability		
Cohort 2							
2A	CCI	After CCI	CCI Active CCI Placebo);	Final determination of dose and dosing regimen by Sponsor	Dose-refinement or additional data	Yes	Yes
2B		After	Active Placebo);	Final determination of dose and dosing regimen by Sponsor	Dose-refinement or additional data	Yes	Yes
2C		After	Active Placebo);	Final determination of dose and dosing regimen by Sponsor	Dose-refinement or additional data	Yes	Yes
2D		After	Active Placebo);	Final determination of dose and dosing regimen by Sponsor	Assess safety, PK and tolerability	Yes	Yes
Cohort 3							
3E	CCI	After Cohort(s) CCI	CCI Active CCI Placebo);	Based on Cohort(s) 1 and/or 2	Additional data in younger participants	Yes	Yes
3F		After Cohort(s) CCI	Active Placebo);	Based on Cohort(s) 1 and/or 2	Additional data in younger participants	Yes	Yes

Table 1. Cohort Details

Cohort	Age Band	Timing of Cohorts	Size*	Dose	Objective	Optional Cohort	E-DMC Concentration and Safety Review
3B	CCI	After Cohort(s) CCI	CCI Active CCI Placebo);	Based on Cohort(s) 1 and/or 2	Additional data in younger participants	Yes	Yes
3D		After Cohort(s) CCI	Active Placebo);	Based on Cohort(s) 1 and/or 2	Additional data in younger participants	Yes	Yes

* In case of enrollment challenges: minimum CCI Active CCI Placebo); If Sponsor recommends repeating the dose: additional CCI Active: CCI Placebo) permitted

1.3. Schedule of Activities

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

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

1.3.1. SoA

Table 2. SoA

Visit Identifier	Screen	Treatment Period				F/U		ET	Notes
Abbreviations used in this table may be found in Appendix 12 (Section 10.12)	**Day -1 to Day 1**	**Day 1**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Prior to Day CCI**	• **Day relative to start of study intervention (Day 1).** • **CCI visit to collect PK blood sample CCI post dose.**
Visit Window				+1 day	+1 day	±2 days	±2 days	+1 day	
Visit type	CCI								ET: if ET occurs after Day CCI visit, CCI visit allowed (follow Day CCI activities). ET prior to Day CCI should be in person visit (CCI . Day CCI visit can occur in person if needed.
Informed consent(s) for study, and assent (if appropriate)	X								• Informed consent must be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3.
Screen for inclusion/ exclusion criteria	X	X							• See Section 5.1 and Section 5.2. • For Argentina, see Exclusion Criterion 23.
Demographics	X								• See Section 8.1.1.
Registration/ randomization	X	X							• Randomization allowed on day of screening after completion of all screening assessments. • At registration, participant enrollment number and dose level allocation assigned.
Medical History and Physical Examination									

Table 2. SoA

Visit Identifier	Screen	Treatment Period				F/U		ET	Notes
Abbreviations used in this table may be found in Appendix 12 (Section 10.12)	**Day -1 to Day 1**	**Day 1**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Prior to Day CCI**	• **Day relative to start of study intervention (Day 1).** • **CCI visit to collect PK blood sample CCI post dose.**
Visit Window				**+1 day**	**+1 day**	**±2 days**	**±2 days**	**+1 day**	
Visit type	CCI								ET: if ET occurs after Day CCI visit, CCI visit allowed (follow Day CCI activities). ET prior to Day CCI should be in person visit (CCI. Day CCI visit can occur in person if needed.
Medical history including background factors; Appendix 10B#1	X								• See Section 8.1.1 and Appendix 10B#1 in Section 10.10.2.
Collect social factors; Appendix 10B #2	X					X	X	X	• See Appendix 10B#2 in Section 10.10.2.
Physical Examination (recorded in source document)	X	X		X	X	X		X	• Day 1 complete physical exam pre-dose. • After Day 1, brief physical exam. • See Section 8.3.1. • See Appendix 10C in Section 10.10.3 for suggested chronology of assessments.
Body Weight	X					X		X	• See Section 8.3.1.
Length / Head Circumference	X								• See Section 8.3.1.
Vital signs including SpO_2	X	X		X	X	X		X	• Before PK, NP swabs and IMP administration (See Appendix 10C in Section 10.10.3 for proposed chronology of assessment). • If hospitalized collect oncedaily until discharge and per SoA after discharge. See Section 8.3.2.
12-Lead ECG	X								• ECG may be performed after screening as needed per investigator discretion. • See Section 8.3.3 for ECG details. • See Appendix 10C in Section 10.10.3 for proposed chronology of assessment.
Record Supplemental O_2 need	X	X	X	X	X	X	X	X	• See Section 8.3.2.3.

Table 2. SoA

Visit Identifier	Screen	Treatment Period				F/U		ET	Notes
Abbreviations used in this table may be found in Appendix 12 (Section 10.12)	**Day -1 to Day 1**	**Day 1**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Prior to Day CCI**	• **Day relative to start of study intervention (Day 1).** • **CCI visit to collect PK blood sample CCI post dose.**
Visit Window				**+1 day**	**+1 day**	**±2 days**	**±2 days**	**+1 day**	
Visit type	CCI								ET: if ET occurs after Day CCI visit, CCI visit allowed (follow Day CCI activities). ET prior to Day CCI should be in person visit (CCI. Day CCI visit can occur in person if needed.
Lab Assessments									• See Section 8.3.4 for blood volumes and additional information. • See Appendix 2 in Section 10.2 for Clinical Laboratory tests to be done. • For laboratory collection volumes, see Section 8.3.4.
RSV Diagnostic Test	X								• Within CCI hours of randomization See Sections 5.1, 8.1.
Safety Labs (CBC, Chemistry	X	X		X	X			X	• CCI cohort CCI : liver function (AST, ALT, T bili) must be reviewed prior to Day CCI dosing. • All other cohorts (CCI days old) should have the Day 1 pre-dose liver function tests (AST, ALT, T bili) ordered stat, if possible. • Safety labs can be done at screening or pre-dose on Day 1. • Pre-dose (Screening/Day 1) protocol-specified safety labs do not need to be repeated if performed as part of standard of care within 24 hours prior to first dose on Day 1. This includes labs conducted prior to signing of the ICD and these lab results will be entered in the CRF for the Screening/Day 1 visit. • Day CCI and/or Day CCI safety labs completed within the study specified window for that visit, do not need to be timed with the PK sample collection. • If Day CCI safety labs are done on Day CCI blood volume allowances should be reviewed prior to Day CCI lab collections (see Table 7). • If ET occurs after Day CCI visit, safety labs not required.
UA	X	X							• UA can be collected either at screening or Day 1, and at any time during the visit.

Table 2. SoA

Visit Identifier	Screen	Treatment Period				F/U		ET	Notes
Abbreviations used in this table may be found in Appendix 12 (Section 10.12)	**Day -1 to Day 1**	**Day 1**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Prior to Day CCI**	• **Day relative to start of study intervention (Day 1).** • **CCI visit to collect PK blood sample CCI post dose.**
Visit Window				**+1 day**	**+1 day**	**±2 days**	**±2 days**	**+1 day**	
Visit type	CCI								ET: if ET occurs after Day CCI visit, CCI visit allowed (follow Day CCI activities). ET prior to Day CCI should be in person visit CCI . Day CCI visit can occur in person if needed.
PK Blood Sample				X	X			X	• See Appendix 10C in Section 10.10.3 for suggested chronology of assessments. • Day CCI and Day CCI PK schedule in Table 3. • Day CCI: If post-dose PK labs at CCI post-dose is not collected on Day CCI these post-dose PK labs must be collected on Day CCI Day CCI: PK pre-dose lab may be timed with safety labs to minimize blood draws. • If ET occurs after treatment period, PK sample does not need to be collected. • See Section 8.5.
Study Intervention and Other Treatments									
Prior/concomitant treatment(s)	X	X	→	→	→	→	X	X	• See Section 6.9.
IMP administration		X	X	X	X				• CCI losing Days 1 to CCI or CCI (Total CCI doses). • IMP (one dose) to be administered to participant during visit on Day 1, Day CCI and Day CCI • For the day of extended post dose PK collection (Day CCI or Day CCI), the dose administered at visit must be in the morning for participants in an outpatient setting. • See Section 6. • See Appendix 10C in Section 10.10.3 for suggested chronology of assessments.

Table 2. SoA

Visit Identifier	Screen	Treatment Period				F/U		ET	Notes
Abbreviations used in this table may be found in Appendix 12 (Section 10.12)	**Day -1 to Day 1**	**Day 1**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Prior to Day CCI**	• **Day relative to start of study intervention (Day 1).** • **CCI visit to collect PK blood sample CCI post dose.**
Visit Window				**+1 day**	**+1 day**	**±2 days**	**±2 days**	**+1 day**	
Visit type	CCI								ET: if ET occurs after Day CCI visit, CCI visit allowed (follow Day CCI activities). ET prior to Day should be in person visit CCI. Day CCI visit can occur in person if needed.
Study kit dispensed from IRT and parent(s)/legal guardian instructed on its use		X							• Parent or legal guardian review of dosing video, dosing instructions and training of IMP administration on Day 1, or prior to discharge if hospitalized, and subsequently as needed. If parent or legal guardian is allowed to administer study drug while hospitalized, per local regulations, training should occur prior to parent or legal guardian study drug administration. • Parent or legal guardian should be taught on Day 1 or prior to going home if hospitalized, how to prepare the dose and demonstrate understanding, under the supervision of the HCP.
IMP compliance		X	X	X	X	X			• Day CCI visit – Retrieval of used and unused IMP bottles after completion of Day CCI dosing, as applicable. • Review eDiary compliance daily. • See Section 6.5.
Assessments									
RSV-associated signs and symptoms (collected by HCP)	X	X		X	X	X		X	• Day 1 collected pre-dose. • Collected daily if hospitalized until time of discharge. • Collected if participant has an unplanned in person visit between Days CCI to CCI • See Section 8.2.1.
Palatability assessment for oral dispersion through eDiary by parent(s)/ legal guardian//HCP		X	X	X	X				• Done after each dose. • See Appendix 10D in Section 10.10.4. Also see Section 8.2.2.
Explain eDiary		X							• Explain eDiary completion requirements to participant's parent/ legal guardian and assist with access to the eDiary (such as downloading the app or issue a provisioned device, if required).

Table 2. SoA

Visit Identifier	Screen	Treatment Period				F/U		ET	Notes
Abbreviations used in this table may be found in Appendix 12 (Section 10.12)	**Day -1 to Day 1**	**Day 1**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Day CCI**	**Prior to Day CCI**	• **Day relative to start of study intervention (Day 1).** • **CCI visit to collect PK blood sample CCI post dose.**
Visit Window				**+1 day**	**+1 day**	**±2 days**	**±2 days**	**+1 day**	
Visit type	CCI								ET: if ET occurs after Day CCI visit, CCI visit allowed (follow Day CCI activities). ET prior to Day should be in person visit (CCI). Day CCI visit can occur in person if needed.
Record RSV related Medical Visits	X	X			X	X	X	X	• RSV related medical visits a participant has attended since the last assessment will be collected. Medical visits include those provided by an HCP: outpatient or inpatient visit, emergency room or urgent care visit. • See Section 8.3.5.
Serious and nonserious AE monitoring	X	X	→	→	→	→	X	X	
Biomarker Assessments									**See laboratory manual.**
RSV RNA Assessments (NP)		X		X	X	X	[X]	X	• Day NP swab sample is collected pre-dose for RSV RNA assessment and CCI (See Section 8.7). • For NP swabs collected post-Day 1 (See Section 8.7). • If participant has an unplanned in person visit between Days CCI through Day CCI or an in person visit for the Day CCI visit, an NP swab [X] may be collected for RSV RNA assessment at PI and parent discretion (See Section 8.7).

1.3.2. Multiple Dose PK Days (For All Cohorts)

Table 3. Multiple Dose PK Days (For All Cohorts)

Visit Identifier	Treatment Period				Notes
Study Day (window)	Day [redacted] (+1)			Day [redacted] (+1)	[redacted] visit to collect PK samples up to [redacted] post-dose
Hours After Morning Dose	0	[redacted]		0	Hour 0 = pre-dose sample collection
Study intervention administration	X			X	
PK blood sample		X	X	X	• Day [redacted] If post-dose PK labs at [redacted] post-dose are not collected on Day [redacted] these post-dose PK samples must be collected on Day [redacted] • Day [redacted] pre-dose PK collection only and can be timed with safety lab collection

2. INTRODUCTION

Sisunatovir (PF-07923568, formerly RV521) is a potent inhibitor of RSV F protein mediated cell-to-cell fusion that is currently being investigated in participants with RSV LRTI.

2.1. Study Rationale

The purpose of this study is to establish safety, tolerability, PK, and guidance for dosing of sisunatovir in a pediatric population (1 day up to 60 months of age) with RSV-LRTI for further clinical development of sisunatovir. This study will provide additional safety, tolerability and PK data at ages previously evaluated in C5241003 to inform dose selection in future studies and will also provide this data in a broader pediatric population (CCI [redacted] old and children CCI [redacted] old) to inform dose selection in future studies. Palatability assessments will also be conducted to aid in the development of pediatric formulations of sisunatovir.

2.2. Background

RSV is ubiquitous and is known to infect almost all children by 2 years of age [1]. The clinical manifestation of RSV infection is typically mild upper respiratory tract illness. However, in infants, young children, immunocompromised and the elderly, it can cause severe LRTI. In a systematic analysis of the global RSV disease burden in 2019, an estimated 33 million episodes of acute LRTI and 3.6 million acute LRTI hospitalizations were attributed to RSV disease in children less than 5 years old [2]. At least 101,000 deaths worldwide were reported in children <5 years of age, with a substantial burden of severe cases and fatalities occurring in children below 6 months of age and in those residing in low- and middle-income countries. Infants <6 months of age are noted to be at the highest risk of severe RSV disease, which can lead to hospitalization, ICU admission and even death [3,4].

The current management of RSV infection includes limited treatment measures, primarily consisting of supportive care, and preventative measures. There is only one antiviral approved, ribavirin, a nucleoside analogue, but clinical use is restricted due to its limited antiviral potency, delivery route, toxicity and teratogenic potential [5]. Preventative measures for pediatric RSV include 2 monoclonal antibodies and the maternal RSV vaccine. The monoclonal antibody Synagis (palivizumab) interacts with F glycoprotein of the RSV virus and is approved in the US, EU [6,7] and other countries. Palivizumab has been shown to provide protection in infants at risk of severe disease, but needs to be given before infection and is administered monthly throughout the winter season [7]. It is approved for use in infants with a history of prematurity, hemodynamically significant cardiac disease, or chronic lung disease of prematurity. In November 2022, Nirsevimab, a monoclonal antibody to the RSV fusion (F) protein that has an extended half-life, was approved for prevention of RSV-LRTI in newborns and infants during their first RSV season in the EU[8]. Approval was expanded the US in July 2023 where neonates and infants are eligible during their first RSV season, and those <24 months of age are eligible if they remain vulnerable during their second season[9]. Abrysvo is the first RSV vaccine indicated for passive immunization of infants from birth through 6 months of age following administration of the vaccine to the mother during pregnancy. While monoclonal antibodies and maternal RSV vaccination are aimed at prevention of RSV disease, there remains an ongoing unmet clinical need for an

effective therapy for RSV disease in children, and a number of new treatments are in development.

Sisunatovir is a new oral, non-biologic treatment that targets the RSV F protein. Approved prophylactic monoclonal antibodies (Palivizumab and Nirsevimab) [7] [8] in certain countries also target the RSV F protein. Sisunatovir (PF-07923568) is a potent inhibitor of RSV F protein mediated cell-to-cell 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-LRTI. Thus, sisunatovir may provide clinical benefit to pediatric participants with RSV disease.

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

2.2.1. Nonclinical Pharmacology

In vitro, sisunatovir has demonstrated potent inhibition of CCI [redacted] Sisunatovir treatment resulted in a significant reduction CCI [redacted].

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

CCI [redacted]

See the current IB for further details.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In animal pharmacokinetic studies sisunatovir showed prolonged time to 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 [redacted], 0.226, 0.0593, CCI [redacted] and 0.198 in mouse, rat, dog and guinea pig, and human respectively. Following single oral dose and under conditions of steady state dosing in the rat, sisunatovir demonstrates extensive distribution to the lungs resulting in high lung to plasma ratio.

Sisunatovir is a substrate of CCI [redacted] efflux and is metabolized primarily by CCI [redacted]

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

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

Sisunatovir was discovered and initially developed through Phase 2 by ReViral Ltd., which became a wholly owned subsidiary of Pfizer on 09 June 2022.

To date, 9 clinical studies have been completed with sisunatovir; a total of 264 healthy adult participants (not counting the 12 participants from the palatability study who did not swallow sisunatovir) 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.

In an RSV challenge study (C5241002), sisunatovir treatment resulted in a statistically significant reduction in AUC of RSV viral load compared with placebo; 55.25% (p=0.007) and 63.05% (p=0.002) for the 200 mg and 350 mg sisunatovir dose groups respectively (dosed q12h for 5 days). Results for the AUC of total symptom score were consistent with the viral load AUC. Geometric mean AUCs of total symptom score were 195.56, 30.79- and 31.76-hours × 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.

There are 7 ongoing studies:

- A Phase 1 multiple site study (C5241012) in adults 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) in adults 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. In the adult healthy participants treated to date, the occurrence of TEAEs considered related to sisunatovir has been low. The most commonly reported all causality TEAEs (≥10 participants) in the multiple dose studies with sisunatovir in adults were : diarrhea, nausea, abdominal pain, and headache. These TEAEs have been mild to moderate in intensity and resolved without sequelae.

In the pediatric study C5241003 19 participants were enrolled in Part A (single dose) and 32 participants were enrolled in Part B (multiple dose). In Part A 13 TEAEs were reported by 11 (57.9%) participants, of which 5 TEAEs reported for 5 (26.3%) subjects were considered

treatment-related (thrombocytosis (1), sinus arrhythmia (1) and vomiting (3)). All TEAEs were of mild or moderate intensity. During Part B of the study, 38 TEAEs were reported by 12 (38.7%) participants, of which 3 TEAEs reported for 3 (9.7%) participants were considered treatment related (vomiting, diarrhoea and thrombocytosis (1 each)). All TEAEs were of mild or moderate intensity. In both Part A and Part B, no clinically significant trend was observed in clinical laboratory parameters, vital signs, or ECG results. Please see the IB for further information.

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

In adults, sisunatovir is slowly absorbed reaching maximum plasma concentrations (t_{max}) at [redacted] hours with a relatively moderate clearance, resulting in a half-life of [redacted] hours in healthy participants, resulting in steady state concentrations being reached after approximately [redacted] days of dosing and a [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}.

The effect of food on the single dose pharmacokinetics was assessed for the [redacted] For the [redacted] the extent of systemic exposure to sisunatovir (geometric mean AUC_{inf} under fed and fasted conditions) was 357 and 221 ng•h/mL respectively, with the between-subject variability being [redacted] under fed conditions (CV [redacted]% compared with [redacted]%). The ratio of fed/fasted was [redacted]% (90% CI: [redacted]% - [redacted]%) for C_{max} and [redacted]% (90% CI [redacted]% – [redacted]%) for AUC_{inf}. It should be noted that the [redacted] fasted results from C5241001 were [redacted] than typically seen in other studies with [redacted] mg administered under fasting conditions, resulting in an [redacted] ratio of fed/fasted in this study. For the [redacted] the extent of systemic exposure to sisunatovir (geometric mean AUC_{inf}) under fed and fasted conditions was [redacted] ng•h/mL respectively, with the between-subject variability being [redacted] under fasted conditions (CV [redacted]% compared with [redacted]%). The ratio of fed/fasted was [redacted]% (90% CI: [redacted]% – [redacted]%) for C_{max} and [redacted]% (90% CI: [redacted]% – [redacted]%) for AUC_{inf}.

Study C5241004 demonstrated that the disposition of sisunatovir is affected by [redacted] Furthermore, sisunatovir was demonstrated to be [redacted] so dose adjustments for compounds that are [redacted] may need to be considered.

No participant in study C5241001 had a QTcF interval change from baseline >30 ms. 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 concentration response analyses did not identify a QT prolongation signal of potential clinical concern (PMAR-EQDD-C524b-Pre-Poc-1664).

The preliminary results from a DDI study of sisunatovir tablets (adult formulation) in coadministration with an acid reducing agent showed a significantly reduced plasma exposure (C5241017). These new findings do not represent a safety concern; however, the reduced plasma exposure may have a potential impact on the efficacy of sisunatovir tablets.

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 safety and tolerability data from the first in human studies, provide rationale for the continued investigation of sisunatovir. The purpose of this study is to establish safety, tolerability, PK and guidance for dosing of sisunatovir in a pediatric population (up to 60 months) with RSV-LRTI.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sisunatovir is available in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1.1 for a complete description of SRSDs.

Currently, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2. The clinical impact of these potential risks will be minimized through standard, intensive, patient monitoring of the participants following administration of multiple oral doses of the study intervention.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention: 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.
Gastrointestinal effects	CCI In completed clinical studies sisunatovir has been associated with mild or moderate GI AEs.	Participants will be closely evaluated to monitor for GI AEs.
Cardiovascular effects	CCI . To date, Phase 1 studies in healthy adult participants and a Phase 2 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 thorough QT study (C5241015) was conducted to assess the effect of sisunatovir on QT interval. The concentration-response analyses between sisunatovir exposure which cover a concentration range up to approximately 1.2-fold the high clinical exposure and 3.5-fold the projected therapeutic mean C_{max} concentration studied in Phase 1/2 studies and the ΔΔQTcF and HR, did not identify signal of potential clinical concern (ie, QT prolongation).	Monitoring will include vital signs, and baseline as well as event driven ECG assessments. Exclusion of participants with any clinically significant ECG abnormality in a participant's medical history, or in the pre-dose ECG that per investigator judgement may affect participant safety or interpretation of study results.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
CCI interactions may be a CCI for the study.	Vital signs and a physical examination CCI be performed during CCI interactions, which may miss clinically relevant signs. Digitally illiterate parent(s)/legal guardian or parent/legal guardian with limited internet access may be excluded.	The CCI visit on Day CCI allows the HCP to monitor the participant's wellbeing CCI requiring the participant to CCI the site. There is an in person visit the next day (Day CCI and any adverse event assessed by CCI can be appropriately actioned. Ediary that includes Dosing questionnaire can be done at home and therefore not impacted with Day CCI as CCI visit. Site can monitor dosing compliance. Day CCI site visit is allowed, if needed as well. CCI visit is optional at Day CCI however, site visit allowed per investigator discretion. Inclusion #6 requires parent(s)/legal guardian to comply with all scheduled visits, investigational plan, laboratory tests and other study procedures and should be available for telephone contact with site staff for the duration of the study.
IMP preparation and administration is a multi-step process that can impact compliance, and if incorrectly done, may impact the study data.	IMP administration is age and weight based. IMP dispensed in bottles needs to be dispersed in the right volume of diluent by the parent(s)/legal guardian/ HCP as applicable (Section 6.1 and Section 6.2). The prepared IMP in the diluent is a dispersion and can impact the planned dose given to the participant. CCI and CCI are not permitted CCI for the study	Training instructions and videos on IMP preparation and administration will be provided to investigators, site staff and parent(s)/legal guardian. For outpatient participants, IMP administration during visit on Days CCI will be done by parent(s)/legal guardian under the observation of the HCP. For Inpatient participants, IMP administration will be done by the HCP, or by parent(s)/legal guardian, if permitted by local policy. CCI may be the diluent for CCI participants and may minimize risk of CCI to CCI if this is used as a diluent. For infants, the volume of the study intervention will be a small volume compared to volume of an infant's

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		feed (up to 5.4 mL, based on 95th percentile weight for a 2-year-old).
Impact to participant with regard to study participation, including assessments and visits.	Clinical management of participant when there is worsening of RSV infection resulting in hospitalization. Continuing in the study when participant is enrolled as an inpatient and is discharged later. Study Day [redacted] or [redacted] requires an extended stay at the site (if the participant is outpatient at the time of visit) can be especially challenging. Discomforts/concerns during study conduct for assessments including ECG, nasal swabs, blood draws and blood volumes.	Selection of sites with capabilities that allow for management of participants with changes from an outpatient to inpatient or inpatient to outpatient settings. CCI [redacted] on Day [redacted] or [redacted] mitigate the challenges with an CCI [redacted] for participants in the outpatient setting. For the 5-week duration of the study, the assessments, including blood draws and NP swabs, have been kept to a minimum for all cohorts where feasible. There are currently no approved RSV antivirals and thus providing placebo does not lead to additional risks for the participant. The efficacy of sisunatovir is still being evaluated. All participants (placebo or sisunatovir) will continue to receive standard of care.

2.3.2. Benefit Assessment

The proposed doses in this study are targeting steady-state exposures comparable to CCI mg CCI in adults, which were found to robustly decrease viral load and alleviate RSV symptoms relative to placebo (C5241002). On this basis, the potential benefit to individual study participants who receive active treatment may include a shorter time to clinical recovery, prevention of hospitalization, and a lower probability of progressing to more severe illness or death. The potential benefit of the study is that it may provide a new treatment option for pediatric participants with RSV-LRTI.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account an unprecedented surge in pediatric RSV infections during 2022-2023, an unmet need for treatment of RSV infection, and the measures to minimize risk to study participants, the potential risks identified in association with sisunatovir in this dose-finding study are justified by the anticipated benefits in the clinical development of sisunatovir for the pediatric population with RSV-LRTI.

There are currently no approved RSV antivirals available, and thus no active control can be proposed as comparator. The comparator for this study is participants receiving placebo. Each cohort evaluated in the study will have participants on placebo. The placebo group is required for assessing the safety, tolerability, and palatability of the study intervention. All participants (including participants receiving placebo) enrolled in the study will receive the SOC.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the safety and tolerability of sisunatovir compared to placebo in participants with RSV-LRTI.	• Incidence of TEAEs. • Incidence of AEs and SAEs leading to discontinuations. • Incidence of clinically significant abnormal laboratory values and vital signs.	• Not applicable
Secondary:	**Secondary:**	**Secondary:**
To characterize the PK of sisunatovir in participants with RSV-LRTI.	• Plasma concentrations of sisunatovir at steady state (Day CCI or later).	• Not applicable
Tertiary:	**Tertiary:**	**Tertiary:**
To describe the viral load in NP samples over time in participants with RSV-LRTI.	• Viral load measured via RT-qPCR in NP swabs over time (including but not limited to change from baseline at each sampled visit and proportion of	• Not applicable

Objectives	Endpoints	Estimands
	participants with BLOQ at Day [redacted]	
To describe signs and symptoms assessed by HCP over time in participants with RSV-LRTI	• Signs and symptoms over time (including but not limited to change from baseline at Day [redacted] and proportion of participants with each sign at Day [redacted]	• Not Applicable
To assess the overall palatability of prepared oral dispersion in participants with RSV-LRTI	• Responses to palatability questionnaire (eg, participant response to medication) at all time points (specified in protocol).	• Not applicable
CCI [redacted]	• CCI [redacted] • Viral load in NP swabs and RSV signs and symptoms over time in -participants CCI [redacted]	• Not applicable

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, double-blind, sponsor-open, placebo-controlled, multicenter study in RSV-infected outpatient and hospitalized neonates, infants, and children, aged 1 day up to 60 months of age with RSV-LRTI; this is a dose finding study to evaluate the PK, safety, and tolerability of sisunatovir.

CCI [redacted]

- Cohorts 1 and 2:

A: CCI [redacted]
B:
C:
D:

- Cohort 3:

E: CCI [redacted]
F:
B:
D:

Although neonates are defined by the WHO as 0-27 days old [10] [redacted]

Sisunatovir or placebo will be administered [redacted] in a [redacted] ratio, for a period of [redacted] for all cohorts. Each cohort will enroll [redacted] participants in each dose group ([redacted] active: [redacted] placebo). In case of recruitment challenges for any cohort in the study, a minimum of [redacted] participants will be enrolled ([redacted] active: [redacted] placebo).

Sisunatovir doses expected to produce systemic steady-state exposures comparable to the [redacted] mg [redacted] adult dose will be evaluated in dosing Cohort 1. Cohorts 1A, 1B, and 1C will initiate in parallel. [redacted] will receive sisunatovir or placebo, expected to produce systemic steady-state exposures comparable to the [redacted] mg [redacted] in adults. The [redacted] may be enrolled only after E-DMC review of Cohort [redacted] data.

Based on analysis of PK and safety data from Cohort 1, the optional Cohort 2 (2A, 2B, 2C, 2D) may be used for further dose refinement to more closely match the [redacted] mg dose in [redacted] or to gather additional data on doses used in Cohort 1. The dose for Cohort [redacted] will be based on Cohort [redacted]. Only [redacted] will be enrolled [redacted] in [redacted] Dose regimens for Cohort 2 will be provided via a digital system (eg, IWRS) upon incorporation of additional data from adults (C5241006) into the PopPK model and conducting simulations. Doses in Cohort 2 will not exceed exposures found to be well tolerated in adults in Study C5241006.

The optional Cohort 3 (3E, 3F, 3B, 3D) may be used if additional data (exposure, safety, tolerability data) for a given dose in one or more of the [redacted] is needed. The [redacted] in Cohort 3 focus on those ages most susceptible [redacted] (less than [redacted]. The specific dose and [redacted] in the optional Cohort 3 will be determined upon review of Cohorts 1 and/or 2 PK and safety data but will not exceed exposures found to be well tolerated in adults in Study C5241006. Sponsor will determine which age groups in Cohort 3 need additional exposure, safety or tolerability data for a given dose. Dose regimens for Cohort 3 will be provided via a digital system (eg, IWRS).

The Sponsor will make the final decision of doses for the cohorts, including recommendation to repeat a dose or opening enrollment of the subsequent cohort. An independent external data monitoring committee (E-DMC) will review the unblinded safety and concentration data after completion of Day [redacted] visit for each cohort (approximately [redacted] participants, [redacted] participants if there are recruitment challenges) to ensure the safety of participants. The E-DMC approval of Sponsor's recommendation will be independently assessed for each of the different age groups and will be based on the safety/tolerability and concentration data (ie, [redacted]). In the event that there is a safety signal of concern, all randomizations must be halted by the Sponsor until the E-DMC has completed their review and has recommended that further randomization may continue. An earlier meeting of the E-DMC can be convened, as warranted, and based on the results of the E-DMC review, the E-DMC may recommend to the Sponsor that a dose of sisunatovir be terminated. If Sponsor recommends repeating the dose, an additional [redacted] participants receiving active drug and

[redacted]placebo may be enrolled in the same age group within the same cohort (limit once per cohort).

Participants may be replaced at Sponsor discretion for the following reasons: if the participant's parent(s)/legal guardian withdraws consent, if the participant misses any dose before providing the [redacted] sample on Day [redacted] or [redacted] if the participant misses any PK samples, if IMP is discontinued, or if the participant's RSV test results at screening are not confirmed by the central laboratory RSV test result, if participant was exposed to a prohibited concomitant medication or if Day 1 RSV RNA level by RT-qPCR is less than the lower limit of quantification.

Participant(s) with discrepant central laboratory RSV test result will not be included in the primary analysis.

For each participant, the study will have a maximum duration of approximately 5 weeks. This includes a screening period of 1-2 days, a [redacted] day Treatment period and a [redacted] follow-up period [redacted] The highest, well-tolerated dose will be determined for the corresponding age band in this study.

Approximately a maximum of 108 participants [redacted] in each cohort + [redacted] additional in each cohort if necessary) will be enrolled. The minimum number of participants (based on a minimum of [redacted] participants per Cohort) is approximately [redacted] evaluable participants as Cohorts 2 (2A, 2B, 2C) and 3 (3E, 3F, 3B, 3D) are optional in the study.

The study will be conducted as a double-blind, sponsor-open study and will be conducted globally with the number of study sites yet to be determined-. No study intervention will be provided to participants at the end of their study participation (Section 6.7).

4.1.1. Dose Finding and Stopping Rules

The Sponsor will make the final decision of doses for the cohorts, including recommendation to repeat a dose or opening enrollment of the subsequent cohort. The E-DMC approval of the Sponsor's recommendation to repeat a dose or opening enrollment of the subsequent cohort will be independently assessed for each of the different age groups and will be based on the safety/tolerability and concentration data.

Repeat dosing at the assessed dose level or progression to the higher dose level will not occur if:

- Mean C_{max} [redacted] ng/mL and Mean AUC_{24} [redacted] ng•h/mL, within an age band ([redacted])

Dosing or enrollment interruption will occur if any of the following is observed:

- Death of a participant during participation in the study receiving study intervention (sisunatovir) and assessed as possibly, probably, or definitely related to study intervention (sisunatovir) by the Investigator(s) and/or Sponsor.
- Two or more SAEs in the same SOC in the study receiving study intervention (sisunatovir) assessed as possibly, probably, or definitely related to study intervention (sisunatovir) by the Investigator(s) and/or Sponsor.
- Severe nonserious AEs, considered as, at least, possibly related to study intervention (sisunatovir), in 2 participants (receiving sisunatovir), independent of within or not within the same organ class, indicating dose limiting intolerance.
- Two or more participants receiving study intervention (sisunatovir) experience the same or a similar AE that is assessed as severe in intensity and in the opinion of the E-DMC and/or Sponsor, represent an unacceptable risk to participants enrolled in the trial.
- If two or more participants receiving study intervention (sisunatovir) develop similar clinically significant laboratory, or vital sign abnormalities, in the same organ class, indicating dose limiting intolerance.

If any of the above criteria are fulfilled, restart of dosing will only be possible if agreed by the E-DMC. Should a clear non-IMP cause for any of the above be identified, the study may continue.

4.2. Scientific Rationale for Study Design

This study is a randomized, double-blind, sponsor-open, placebo-controlled, multicenter study in RSV-infected outpatient and hospitalized neonates, infants, and children, 1 day up to 60 months of age with RSV-LRTI. This is a dose finding study to evaluate the PK, safety, and tolerability of sisunatovir. The current study will provide additional data at ages previously evaluated in C5241003 and will also evaluate a broader pediatric population (CCI [redacted] old and children CCI [redacted] old) to inform dose selection in future studies. Since children are a vulnerable population, an E-DMC is used in this study to ensure the safety of participants.

The safety and PK of sisunatovir have not been studied to-date in CCI [redacted] but this CCI [redacted] group is noted to be at the CCI [redacted] [3,4]. Additionally, expanding the safety and PK information of sisunatovir CCI [redacted] to inform future studies can help ensure correct dose regimens to help prevent acute LRTI hospitalization attributed to RSV disease in children less than 5 years old [2].

There are currently no approved RSV antivirals available, and thus no active control can be proposed as comparator. The comparator for this study is participants receiving placebo. Each cohort evaluated in the study will have participants on placebo. The placebo group is required for assessing the safety, tolerability, and palatability of the study intervention. All

participants (including participants receiving placebo) enrolled in the study will receive the SOC.

According to the DDI risk assessment for sisunatovir as described in Section 2.2.2, sisunatovir is a CCI [redacted] of CCI [redacted] For this reason, sensitive CCI [redacted] are prohibited in this study. Since sisunatovir is a CCI [redacted] are also prohibited. Lastly, due to potential risk of CCI [redacted] inhibition, sensitive substrates of these transporters may be administered with caution during treatment period.

4.2.1. Patient Input Into Design

Parental surveys are being conducted to evaluate feasibility of study recruitment, optimize study participation, and collect feedback on how to enhance potential educational materials available for participant's parent(s)/legal guardians.

4.2.2. Diversity of Study Population

Diversity of study population in this protocol applies to sites in the US only. The diversity strategy will include sites with the potential to support the recruitment of diverse pediatric populations. Reasonable attempts will be made to enroll participants that are representative of the patient population that will be treated with sisunatovir in clinical practice. The following strategies may be explored in support of diverse recruitment efforts:

- Selecting sites that have access to diverse pediatric participants
- Creating and completing individual site recruitment plans in collaboration with sites
- Have proactive discussions with investigator sites throughout the enrollment period to assess and reevaluate site specific strategies as needed to best position each site for the most diverse representation enrollment outcomes
- Developing recruitment and retention materials with culturally and linguistically appropriate language and imagery to resonate with underrepresented populations
- Translating all patient-facing materials into US Spanish
- Providing investigators with recruitment materials for both potential participants and other Healthcare Providers
- Educating site staff on the importance of including diverse participants
- Monitor diverse enrollment to identify potential opportunities to include diverse populations

4.2.3. Rationale for Comparator

There are currently no approved RSV antivirals available, and thus no active control can be proposed as comparator. The comparator for this study is participants receiving placebo. Each cohort evaluated in the study will have participants on placebo. The placebo group is required for assessing the safety, tolerability, and palatability of the study intervention.

All participants (including participants receiving placebo) enrolled in the study will receive the SOC. Participants enrolled in the study while in the outpatient setting may continue in the study if hospitalized at investigator discretion. C5241003 study that completed recruitment, was conducted to characterize the PK profile, safety and virologic response to sisunatovir in RSV-infected hospitalized children aged 1 month - 36 months and included an open-label Part A (1.0, 2.0 and 2.5 mg/kg single dose) and double-blind Part B (CCI [redacted]; 2.5 mg/kg, 3.5 mg/kg and 5 mg/kg q12h × 5 days). Initial pediatric dose recommendations for Cohort 1A, 1B, and 1C are based on observed concentrations in Study C5241003 with interpolation of predicted exposures, relative to exposure of CCI [redacted] mg CCI [redacted] in adults.

4.3. Justification for Dose

The current study will evaluate safety, tolerability, PK, and guidance for future dosing of sisunatovir in a broader pediatric population (1 day to 60 months of age) with RSV-LRTI for further clinical development of sisunatovir.

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 Q12 × 5 days were administered following inoculation of an RSV infection (C5241002). In this study, at both doses evaluated, sisunatovir robustly decreased viral load and alleviated RSV symptoms relative to placebo. While statistically significant differences were not observed between the two dose levels relative to placebo, the 350 mg dose effect was numerically larger than the 200 mg dose. Pediatric doses are expected to produce systemic steady-state exposures comparable to the adult dose of 200 mg q12h that was found to be effective in treating viral load and symptoms of RSV in the challenge study.

Additionally, sisunatovir was administered in a completed ex-US Phase 2 study (C5241003, previously REVC003) to characterize the PK profile, safety and virologic response to sisunatovir in RSV-infected hospitalized children aged 1 month -36 months. Participants 1 month to <6 months of age were administered sisunatovir up to 2.5 mg/kg q12h for 5 days. Participants 6 months to 36 months of age were administered sisunatovir up to 5.0 mg/kg q12h for 5 days. The highest dose in each age group provided mean exposures above EC_{90} and below the pre-specified upper exposure limit of 294 ng/mL. Overall, sisunatovir was found to be safe for infants and children ≥1 month to ≤36 months. These results support the current study to establish safety, tolerability, PK, and guidance for dosing of sisunatovir in a broader pediatric population (1 day up to 60 months) with RSV-LRTI for further clinical development of sisunatovir.

Initial pediatric dose recommendations for Cohort 1A, 1B, and 1C are based on observed concentrations in Study C5241003 with interpolation of predicted exposures, relative to

exposure of CCI mg CCI in adults. The proposed starting dose of sisunatovir for participants CCI is CCI mg/kg and for participants CCI) is CCI mg/kg (see Table 4). These doses are CCI than those administered in CCI , which were well below the PK stopping limit NOAELs.

Table 4. Cohort 1 Dose Recommendations

	CCI (preliminary) GeoMean (%CV)					CCI GeoMean (%CV)
	CCI (n=11)	3.5 mg/kg (n=3)	Predicted CCI	Predicted	5 mg/kg (n=2)	CCI
$C_{troughSS}$	42 (190)	17 (200)			69 (30)	
C_{maxSS}	111 (146)	36 (249)			181 (98)	
AUC_{SS}	869 (121)	264 (224)			1380 (79)	

Based on analysis of PK and safety data from Cohort 1, the doses for Cohort 2 may be adjusted to more closely match the CCI mg dose in CCI or to gather additional data on doses used in Cohort 1. To support this, an iterative population PK model is being developed to support further pediatric dose recommendations. This model is developed with successive updates and validations from all available adult and pediatric data as studies complete, including Part A and B of C5241003. It is anticipated that the weight-based dose will be adjusted for pediatric patients by age, based on maturation of CCI liver function. The CCI dose of sisunatovir for CCI will be determined after evaluation of CCI The specific dose and CCI in optional Cohort 3 will be determined upon review of Cohorts 1 and/or 2 but will not exceed exposures found to be well tolerated in adults (C5241006). Sponsor will determine which age groups in Cohort 3 need additional exposure, safety or tolerability data for a given dose.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study 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 visit 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 the study only if all of the following criteria apply at screening unless otherwise indicated:

Age and Sex:

1. Participants 1 day to ≤60 months of age and weight ≥2.5 kg to ≤23 kg.

Disease Characteristics:

2. A positive RSV diagnostic test with result available in source document to confirm eligibility either according to routine site practice or Investigator sites may use RSV POC test kits that are provided for this study. RSV diagnostic test, antigen or molecular test is acceptable, and should be collected within [CCI redacted] hours of randomization.

3. Evidence of LRTI by the presence of ≥1 from any of the following 4 categories (a through d):

   a. Increased respiratory rate for age:

   - < 2 months: ≥60 bpm
   - ≥2 to <12 months: ≥50 bpm
   - ≥12 to ≤60 months: ≥40 bpm

   b. SpO_2 < 95% on room air

   c. Increased respiratory effort as evidenced by ≥1 of the following:

   - Grunting with expiration
   - Nasal flaring
   - Retractions

   d. One or more of the following exam findings on auscultation:

   - Wheezing
   - Rhonchi
   - Rales or crackles

4. RSV related signs and/or symptoms must be present for ≤[redacted] days at time of randomization.

Other Inclusion Criteria:

5. The parent(s)/legal guardian of the participant have provided written informed consent for the participant to participate. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal).

6. Participants' parent(s)/legal guardian(s) and participants, as age appropriate, who are willing and able to comply with all scheduled visits, investigational plan, laboratory tests, and other study procedures. Participants' parent(s)/legal guardian should be available for telephone contact with site staff for the duration of the study.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Any medical, developmental, or behavioral condition (including history of self-harmful behaviors) or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Premature infants (gestational age less than 35 weeks) AND <1 year of post-natal age. Note: Infants 35- and 36-week gestational age are permitted if they weigh at least 2.5 kg and are at least 2 months post-natal age.

3. CCI with intrauterine growth restriction defined by having 3 or more of the following:

    - Birth weight <10th percentile on population-based or customized growth charts
    - Head circumference <10th percentile
    - Length <10th percentile
    - Prenatal diagnosis of fetal growth restriction
    - Maternal pregnancy information associated with fetal growth restriction (eg, hypertension, pre-eclampsia)

4. Any clinically significant ECG abnormality in a participant's medical history, or in the pre-dose ECG that per investigator judgement may affect participant safety or interpretation of study results. **Note**: If sinus tachycardia is present, and not worse than expected due to underlying disease, participant may be considered at investigator discretion, if the sinus tachycardia is not expected to interfere with evaluation of response to study intervention.

5. Known history of hepatic disease, concern for active acute or chronic viral hepatitis, or acute hepatic failure.

6. Participants >[CCI] days only: Known history of AST, ALT, or T bili abnormalities >2 × ULN within 6 months of screening. Laboratory assessments not required at screening for participants >[CCI] days unless deemed necessary by the investigator to confirm normal hepatic function. **Note**: Participants with history of elevated bilirubin due to neonatal hyperbilirubinemia that is resolved with T Bili values within reference range may be enrolled.

7. History of epilepsy or seizures. Participants with a history of febrile seizures will be permitted to enroll.

8. Expected to receive or has received an antiviral for another respiratory viral infection (eg, influenza or COVID-19) within 10 days of screening.

9. Suspected or confirmed clinically significant moderate or severe bacterial infection (eg, bacterial pneumonia, bacteremia), that may interfere with the evaluation of response to the study intervention at investigator discretion. Participants with mild, localized infections such as otitis media or UTI can be included.

10. Evidence of severe respiratory failure requiring invasive mechanical ventilation or ECMO. **Note**: Participants requiring non-invasive ventilation, including high flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP), remain eligible for the study.

11. Known to have significant comorbidities, including genetic disorders (eg, trisomy 21); cardiopulmonary diseases (eg, hemodynamically significant congenital heart disease); significant pulmonary disease (eg, cystic fibrosis); history of surgery for diaphragmatic hernia; any hereditary or acquired metabolic diseases, hematological or other malignancy; or is known to be HIV positive; has evidence of severe neurologic impairment or developmental delay that would limit the ability to administer IMP or evaluate the safety or clinical response to IMP. Note: Preterm participants (if <35 weeks gestational age must be at least one year post-natal age) with bronchopulmonary dysplasia (chronic lung disease of prematurity) remain eligible for enrollment.

12. Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications.

- Has received corticosteroids equivalent to prednisone ≥2 mg/kg daily for at least 14 consecutive days within 30 days prior to study start or expected to receive equivalent dose during study drug treatment. Inhaled/nebulized or topical (skin, eyes or ears) corticosteroids are permitted, except those prohibited (see Section 6.9).

- Has received treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study start or expected to receive treatment with these therapeutics during study drug treatment.

13. Malformation of the gastrointestinal tract including unresolved pyloric stenosis, history of necrotizing enterocolitis, short bowel, or other significant condition that would alter drug absorption or increase the risk of diarrhea.

14. Has significant oral and/or maxillofacial malformations that would limit the ability to administer IMP.

Prior/Concomitant Therapy:

15. Allergy to test medication or constituents.

16. Current use of any prohibited concomitant medication(s). Refer to Appendix 8.

    - Has taken within 5 half-lives plus 14 days before dosing, or requires during the dosing period of the study, any drug that could impact the PK of the investigational product, including any prescription medications, OTC medications, herbal remedies or dietary supplements containing St. John's Wort or the consumption of CCI [redacted] products as these are known to be CCI [redacted]
    - Has taken within 5 days before dosing or require during the dosing period of the study, any proton pump inhibitors. Has taken within 12 hours before dosing or require during the dosing period of the study, any H2 blockers.

17. Has received treatment with ribavirin (oral or inhaled) within 30 days of screening.

Prior/Concurrent Clinical Study Experience:

18. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during their participation in this study.
    Note: local regulations or other factors may require more than 30 days.

Diagnostic Assessments

19. Baseline 12-lead ECG with QTcF ≥450 ms.

20. CCI [redacted] old) with any of the following laboratory abnormalities at screening:

    - Total bilirubin >2 × ULN
    - AST >2 × ULN
    - ALT >2 × ULN

Other Exclusion Criteria:

21. Other acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for entry into this study.

22. More than 1 participant per household.

23. For Argentina participants ONLY, as per local regulations, evidence that participant is positive for HIV, HBV, or HCV infection based on mother's serology results during pregnancy or the participant's serologies.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who assent to participate in the clinical study but are not subsequently enrolled 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.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not Applicable

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 or matching placebo.

6.1. Study Intervention(s) Administered

Sisunatovir formulation evaluated in this study is a [redacted], same as the formulation evaluated in the C5241003 study. The matching placebo is formulated as a dry blend of mannitol and microcrystalline cellulose. The dry blends are filled into hydroxypropyl methylcellulose (hypromellose) capsules. Sisunatovir and placebo are administered [redacted] for [redacted] days (2 doses daily Day 1-Day [redacted]) /6 days (if not started with 2 doses on Day 1) for a total of [redacted] doses.

Study intervention will be administered to the participant by a parent, legal guardian, or HCP.

Study Intervention(s)		
Intervention Name	**PF-07923568 (sisunatovir)**	**Placebo for PF-07923568 (sisunatovir)**
Type	Drug	Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	CCI capsule dispersed in CCI for oral ROA or nasogastric tube ROA	Matching Experimental dispersed in CCI for oral ROA or nasogastric tube ROA
Unit Dose Strength(s)*	CCI mg/mL (50 mg sisunatovir CCI into CCI)	Matching Experimental
Dosage Level(s)	Cohort 1A: CCI mg/kg CCI CCI doses Cohort 1B, 1C: CCI mg/kg CCI CCI doses Cohort 1D, Cohort 2, Cohort 3: TBD	CCI ; CCI doses
Route of Administration	Oral or nasogastric tube	Oral or nasogastric tube
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided to sites in blister cards. Site staff will prepare individual doses in bottles for administration. Each blister card and bottle will be labeled as required per country requirement. Blinded	Study intervention will be provided to sites in blister cards. Site staff will prepare individual doses in bottles for administration. Each blister card and bottle will be labeled as required per country requirement. Blinded
SRSD	IB	IB
Current/Former Name(s) or Alias(es)	sisunatovir PF-07923568	Placebo

Study Intervention(s)		
Intervention Name	**PF-07923568 (sisunatovir)**	**Placebo for PF-07923568 (sisunatovir)**
	RV521	

Study Arm(s)		
Arm Title	sisunatovir	Placebo
Arm Description	Participants will receive sisunatovir (dose as indicated in above table); CCI doses, CCI	Participants will receive placebo; CCI doses, CCI

6.1.1. Administration

Administration of study intervention(s) will be performed by parent(s)/legal guardian for outpatient participants.

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff or parent(s)/legal guardian as allowed by local, state, and institutional guidance for inpatient participants.

Following administration of the first dose of study intervention(s), participants will be observed for 30 minutes by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines as needed.

Study personnel will review dose administration requirements with the participant's parent(s)/legal guardian, as appropriate, before administration and throughout the study as necessary. Parent(s)/legal guardian must be trained by the site staff on Day 1, or prior to going home if hospitalized, on the preparation and administration of the study intervention.

The IMP will be provided as blinded kits (sisunatovir or placebo) in accordance with the randomization schedule.

IMP administration will be by oral route, either via syringe by parent(s), legal guardian(s), or the health care professional. To facilitate pediatric administration, the sisunatovir CCI , and a predetermined volume of diluent is added to form a dispersal by the parent(s)/legal guardian/HCP as applicable. After dispersing the CCI in the diluent by shaking, the required dose is taken up into a syringe and then administered to the participant. Each dose should be administered within CCI of randomization for all participants and CCI in accordance with their assigned dosage and dosing regimen. To allow the participant to select a convenient CCI dosing schedule, the timing of dosing for the

second dose may be adjusted slightly but should be taken at least 4 hours after, but no later than CCI after the first dose. The remaining doses should be taken every CCI

IMP should be administered to the participant in a calm state. Feeding within 30 minutes prior to dosing and within 30 minutes after dosing should be recorded in the eDiary.

Instructions CCI will be provided in the IP Manual. Dosing and Administration Instructions will also be included in the IP manual for the parent(s)/legal guardian/HCP to administer the study intervention at the study site, home and hospital as applicable. In addition, parent(s), legal guardian or HCP will be provided with Dosing Instructions, including a training video, in order to aide in dosing at home.

6.2. Preparation, Handling, Storage, and Accountability

The IMP will be stored under ambient conditions between 15°C and 25°C. The CCI in bottle has an CCI shelf life, CCI has a CCI shelf life.

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 site procedures.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participant's parent(s)/legal guardians on the proper storage requirements for take-home study intervention. See the IPM for storage conditions of the study intervention once dispensed.

6. Study interventions should be stored in their original containers until preparation for dispensing begins for a participant.

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's parent(s)/legal guardian, both used and unused, must be returned to the investigator by the participant's parent(s)/legal guardian. **Returned study intervention must not be redispensed to the participant's parent(s)/legal guardians.**

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 obtain blister card using IRT container number, CCI [redacted] and also provide the label with the instructions on the bottle. CCI [redacted] A second staff member will verify the dispensing and instructions on the labels of the documents. The participant's parent(s)/legal guardian should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the unused bottles to the site at the end of the study. The required number of bottles for the study with IMP will be provided to the parent(s)/legal guardian for the study, based on weight-based dose adjusted by age, on the day of randomization if outpatient and on discharge from the hospital if inpatient.

For outpatient participants, each parent(s)/legal guardian will add a defined volume of permitted diluent prior to oral administration on a mg/kg basis to each bottle. After CCI [redacted] in the diluent by shaking, the required dose is taken up into a syringe and then administered to the participant.

If hospitalized, the study personnel will add a defined volume of permitted diluent prior to oral/NG tube administration on a mg/kg basis to each bottle (guidance on the permitted CCI [redacted] diluents will be provided in the Investigational Product (IP) Manual; also see Table in Section 6.1). The required volume of the resultant dispersion will be administered to the participant according to the prescribed dose required.

Prepared dispersion should be dosed within CCI [redacted] hours.

Each participant will be administered the volume required for the age-range specified dose depending on the weight of the participant.

If the participant misses a dose of IMP within the permitted administration window, , the participant's parent(s)/legal guardian should administer it as soon as possible, but no later than [redacted] hours after the time it is usually taken, and resume the normal dosing schedule. 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 ([redacted] doses total).

Sisunatovir and placebo will be prepared by qualified blinded site personnel according to the IPM. The study intervention will be administered in a blinded fashion to the participants.

IMP will be single use.

The following will be recorded in the eDiary (Appendix 10D Section 10.10.4):

- Date, start time of preparation and time of each dose administered
- Administrator of the study intervention: Parent(s)/legal guardian OR HCP
- Route of administration: oral or nasogastric tube for each dose administered
- Information on feeding within 30 minutes before and after dosing
- Palatability questionnaire after every dosing

See the IP Manual for instructions on how to prepare the study intervention for administration.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of 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.

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, sponsor-unblinded study.

6.4.1. Blinding of Participants

Participants and their parent(s)/legal guardian 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 throughout the course of the study.

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

6.4.3. Blinding of the Sponsor

As this is a sponsor -open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose finding decisions, facilitating PK/PD modeling, and/or supporting clinical development.

6.4.4. Sensitive Clinical Data

Sensitive clinical data are data collected in this study that have the potential to unblind a participant's treatment assignment. Access to sensitive clinical data will be restricted to authorized individuals until the study has been unblinded. The following data variables are considered sensitive clinical data: Assigned treatment group (Active versus placebo); PK parameters.

6.4.5. 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 make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. 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 the individual dose is prepared on site, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed at the site as an outpatient, they will receive study intervention directly from the parent(s)/legal guardian under medical supervision.

The date and time of each dose administered will be recorded in the eDiary (Appendix 10D in Section 10.10.4). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested, if applicable.

When participant's parent(s)/legal guardians administer study intervention(s) at home, compliance with study intervention will be assessed at the next consecutive visit. Compliance will be assessed by direct questioning and counting returned bottles with initially dispensed study intervention at the end of the study and documented in the source documents and eDiary. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of study intervention doses dispensed to and administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the CRF.

If the study participant is hospitalized at the time of enrolment and it is identified that they (he/she) could not attend the Day [redacted] and/or Day [redacted] visits if discharged, the investigator may at their (his/her) discretion, if local regulations allow and [redacted] services are not available, keep the participant in the hospital for convenience to ensure Day [redacted] and/or Day [redacted] assessments can be conducted in compliance with protocol requirements.

Participants may be replaced at Sponsor discretion as described in Section 4.1 and Section 9.5.

Any deviation from protocol-specified dosing (eg, missed single dose or partial dose) should be recorded as a protocol deviation and the investigator or designee is to counsel the participant/guardian and ensure steps are taken to improve compliance.

6.6. Dose Modification

Dose modification within a cohort is not allowed. For further details on dose selection for each cohort, see Section 4.1.

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 the prescribed daily dose of study intervention will be considered an overdose. There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician 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 day of the last overdose.

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

Parent(s)/legal guardian should store the study intervention out of reach of children to avoid any situations that could result in overdosing.

6.9. Prior and Concomitant Therapy

- Use of following antiviral will be recorded in the CRF
  - Prior treatment with Nirsevimab

Prohibited Prior Treatments

- Prohibited concomitant medications that may result in DDI (Section 10.8)
- Receipt of corticosteroids equivalent to prednisone ≥2 mg/kg daily for at least 14 consecutive days within 30 days prior to study start.
- Antivirals within 10 days of screening.
- Treatment with ribavirin (oral or inhaled) within 30 days of screening.
- Treatment with biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study start.
- Has taken within 5 half-lives plus 14 days before dosing any drug that could impact the PK of the investigational product, including any prescription medications, OTC medications, herbal remedies or dietary supplements containing St. John's Wort or the consumption of [redacted] as these are known to be [redacted]

- Administration of proton pump inhibitors must have ended 5 days prior to randomization.
- Administration of H2 blockers must have ended at least 12 hours prior to randomization.
- Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Prohibited During the [redacted] Day Study Drug Administration

- Prohibited concomitant medications that may result in DDI (Section 10.8).
- Biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy.
- Antivirals for respiratory tract infection.
- Requires any drug or food that could impact the PK of the investigational product, including any prescription medications, OTC medications, herbal remedies or dietary supplements containing St. John's Wort or the consumption of CCI [redacted] products as these are known to be CCI [redacted]
- Any administration of proton pump inhibitors and H2 blockers is prohibited. The use of antacids (such as calcium carbonate or magnesium hydroxide) is allowed with staggered dosing (ie, not within 3 hours before or after study drug administration).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Death
- Occurrence of an AE or any other condition posing a risk to a participant or jeopardizing a safe continuation of the study treatment for the respective participant (as judged by the investigator, and/or the national coordinators, and/or the Medical Monitor and the study sponsor)
- Missing any dose prior to the CCI [redacted] draw

- Requirement of prohibited concomitant medications during the study (See Appendix 8 in Section 10.8)

- Study terminated by sponsor

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 follow-up visits. Unplanned visits following permanent discontinuation of study intervention, if needed will be conducted per Day [CCI] visit in the SoA. 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

See Appendix 6 in Section 10.6 for kidney safety monitoring guidelines and discontinuation criteria.

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

Differentiating Acute Kidney Injury from DICI:
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.

Screat increase is defined as:

Infants and Children ≥ 28 days old and < 12 years old:
(i) Screat increase ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii)Screat increase ≥1.5 times baseline known or suspected to have occurred within the prior 7 days

Neonates <28 days old:
(i) Screat increase ≥1.5 to 1.9 times from baseline (previous lowest value) known or suspected to have occurred within the prior 7 days OR
(ii) Screat increase ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours.

- Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows in Table 5.

Table 5. Differentiating DIKI and DICI in Pediatric Participants

	AKI (including DIKI) Any one of the below	DICI
Scys & Screat	Simultaneous, confirmed Scys increase of ≥0.3 mg/L and confirmed Screat increase of ≥0.3 mg/dL post-baseline.	Confirmed Screat increase of ≥0.3 mg/dL post-baseline without simultaneous confirmed increase of ≥0.3 mg/L in Scys post-baseline.
Albuminuria	Confirmed albuminuria increase (see Appendix 6, Section 10.6, for Grades A1 to A3 quantitation)	No albuminuria increase
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours (if monitored)	No urine volume decrease

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected or (ii) urine volume (if measured) is <0.5 mL/kg/h for 6 consecutive hours.

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

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Renal function should be evaluated using the appropriate equation or creatinine reference values described in Appendix 6 (Section 10.6). Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

7.1.2. Liver Injury

A participant who meets the criteria of potential DILI (Hy's law) case as described in Appendix 5 in Section 10.5 or if they meet either of the below criteria, will be withdrawn from study intervention.

- Participants >30 days old with finding of pre-dose AST, ALT or T bili >2 × ULN;
- Any participant during study intervention with at least 2 of the following labs AST, ALT or T bili increase by >2 ULN.

7.1.3. ECG Changes

A participant who meets either bulleted criterion 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. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided.

Study treatment may continue unless the investigator/treating physician is concerned about the safety of the participant, or if the participant will be started on an antiviral, in which case study intervention should be discontinued.

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

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request, or at the request of the parent(s)/legal guardian. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow up;
- Death;
- Investigator decision;
- Study terminated by sponsor;

- Withdrawal of consent/assent by parent(s)/legal guardian or by a child who has provided assent during any phase of the study

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

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants/participant's parent(s)/legal guardian should be questioned regarding their reason for withdrawal.

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

If a participant/participant's parent(s)/legal guardian 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 assent (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 assent.

7.2.1. Withdrawal of Consent

Participants/participant's parent(s)/legal guardian 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's parent(s)/legal guardian specifically withdraws consent/assent for any further contact with them or persons previously authorized by the participant's parent(s)/legal guardian to provide this information. Parent(s)/legal guardian s 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/ participant's parent(s)/legal guardian 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/ participant's parent(s)/legal guardian fails to attend a required study visit:

- The site must attempt to contact the participant's parent(s)/legal guardian and reschedule the missed visit as soon as possible. Counsel the participant's parent(s)/legal guardian on the importance of maintaining the assigned visit schedule, and ascertain whether the participant's parent(s)/legal guardian 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's parent(s)/legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's parent(s)/legal guardian's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant's parent(s)/legal guardian continue to be unreachable, the participant will be considered to have withdrawn from the study.

Participants may be replaced at Sponsor discretion as described in Section 4.1 and Section 9.5.

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.

The date of birth will be collected to ensure correct assignment to the age group and critically evaluate the safety profile by age. Local regulations may apply for collection of full date of birth.

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.

ALT, AST, T Bili lab assessments for [redacted] cohort (within 24 hours of screening) and molecular RSV testing conducted as part of the participant's standard of care and obtained before signing of the ICD may be utilized for eligibility purposes provided the procedures

met the protocol specified- criteria and were performed within the time frame defined in the SoA (Section 1.3) and as specified in Section 5.1 and 5.2.

Safety labs conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD, may be utilized for screening or baseline purposes, provided the safety labs met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Screening RSV diagnostic test information done to confirm eligibility should be collected in CRF, if available in source document and this should include type of test (antigen or RT-PCR), date and time of testing,

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.

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

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

The total blood sampling volume for individual participants in this study is approximately up to 3.9 mL for all cohorts (See Section 8.3.4). The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed the amounts specified for the different age groups in Section 8.3.4.

8.1.1. Baseline Procedures

Planned timepoints for collection of medical history, background and social factors (Appendix 10B Section 10.10.2), and demography are provided in the SoA (Section 1.3). These must be recorded in the CRF and should also include information on gestational age, date of birth, age at screening, and days since onset of signs and/or symptoms. Local regulations may apply for collection of full date of birth.

CCI [redacted]

CCI

[redacted]

8.2. Efficacy Assessments

8.2.1. Signs and Symptoms of RSV

Signs and Symptoms of RSV will be collected by the HCP per the SoA (Section 1.3) during scheduled visits. See Appendix 10A (Section 10.10.1).

8.2.2. Dosing and Palatability questionnaire (eDiary)

An eDiary will be provided to the parent(s)/legal guardian/HCP. Participant's parent(s)/legal guardian or HCP will record study intervention administration and the taste attributes of IMP using the Sponsor-provided eDiary that includes the Dosing and Palatability Questionnaire per the SoA (see Appendix 10D in Section 10.10.4).

Staff will review the study eDiary daily during the treatment period as specified in the SoA (Section 1.3).

8.3. Safety Assessments

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

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems including a symptom-directed examination and general condition.

Height and weight will be measured and recorded. Measurement of length and head circumference will be performed for children <2 years of age only. Age-appropriate tools including stadiometers for measuring height in children 2 years of age or older should be used.

A brief physical examination will include, at a minimum, assessments of the cardiovascular system, respiratory and gastrointestinal systems.

Physical examination for respiratory system includes lung auscultation, evaluation of respiratory effort (eg, retractions) and vital signs (respiratory rate and SpO_2).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, except as required in Appendix 10A and SoA. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

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

Vital signs should be measured with age-appropriate tools including, infant and child pulse oximeters attachments for measuring heart rate and oxygen saturation, and pediatric-sized blood pressure cuffs.

8.3.2.1. Blood Pressure and Pulse Rate / Heart Rate

BP and PR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. BP will be assessed using a correct cuff for the arm size.

BP and PR will be taken before blood collection for laboratory tests and consist of a single measurement of PR and BP measurements. The BP and PR readings will be recorded on the CRF.

8.3.2.2. Temperature and Respiratory Rate

Temperature (Tympanic, Rectal or Skin) and RR will be assessed and recorded on the CRF. Avoid rectal temperature assessments in children less than 6 weeks old. Temperature should be assessed using the same method for all study visits. Document the highest respiratory rate at the time of assessment in the CRF.

8.3.2.3. Oxygen Saturation

Oxygen saturation findings collected during the study will be recorded on the CRF including any supplemental O2 requirement. Document the lowest SpO2 value, while on room air if safe and feasible to do so, at the time of assessment in the CRF.

8.3.3. Electrocardiograms

A single ECG will be collected at screening, and as specified in the SoA (Section 1.3) of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

It is recommended that a consistent placement of leads is made throughout the whole duration of the study for the same participant.

In young children, the right ventricle normally extends to the right side of the sternum. To appropriately display right ventricular potentials, ECGs for children in the under five-year age group must include an alternate lead ('V4R') on the right side of the chest, at a point analogous to the left-sided V4.

Precordial leads:

- V1: 4th intercostal space, right sternal border
- V2: 4th intercostal space, left sternal border
- V3: midway between V2 and the placement of V4 in adults (5th intercostal space, left mid-clavicular line)
- V4R: 5th intercostal space, right mid-clavicular line. Use this lead for V4R, must label as such on ECG.
- V5: anterior axillary line, same horizontal plane as V4
- V6: mid-axillary line, same horizontal line as V4

Limb leads:

- Place on top part of arm or leg for less muscle interference
- For restless infants and young children, the Mason-Likar lead placement can be employed: the 4 limb electrodes are placed anteriorly on the left and right shoulder and left and right side of the lower torso to prevent artefact caused by the movement of the arms and legs.

The screening and any unplanned ECG data collected 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 ECG findings with the baseline/Day 1 ECG, or unplanned ECGs, may potentially be AEs (Appendix 7 in Section 10.7) 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 7 in Section 10.7.

8.3.4. Clinical Safety Laboratory Assessments

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

Laboratory safety parameters will be graded according to DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [11].

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 CCI [redacted] should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

See Appendix 5 in Section 10.5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6 in Section 10.6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Table 6 provides the blood volume allowed to be drawn in participants (neonates, infants, and children) up to 60 months of age. All safety labs should be done locally only. Every effort should be made to limit the amount of blood collected from each participant over the duration of the study. The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed the volumes in Table 6. Repeat or unscheduled samples are allowed based on clinical judgment for participant safety or for technical issues with the samples. The total blood volumes for the different age groups take into account the estimated blood volume for participants at the fifth percentile for weight in each of the cohorts [12,13] and total blood volumes. Per these criteria, 1% of total blood volume is allowed to be drawn within 24 hours

and 3% of total blood volume is allowed to be drawn within 4 weeks. These volumes are shown in Table 7 for all cohorts.

A 1-day old child is the youngest subject to be enrolled in the study. It is calculated that a 1-day old child may weigh 2.5 kg and has 90 mL of blood/kg. Therefore, a 1-day old child likely has a total blood volume of 225 mL. Per the criteria of 1% of total blood volume allowed to be drawn within 24 hours and 3% of total blood volume allowed to be drawn within 4 weeks, this equals an allowance of 2.25 mL of blood in 24 hours and 6.75 mL of blood in 4 weeks for a 2.5 kg child.

Table 6. Blood Draw Allowances for Each Age Band

	CCI			
5th Percentile Weight (kg)	3.5	6	8	2.5
Blood Volume (mL/kg)	80	80	80	90
Total Blood Volume (mL)	280	480	640	225
24 hour max = 1% (mL)	2.8	4.8	6.4	2.25
4 week max = 3% (mL)	8.4	14.4	19.2	6.75

Table 7. Volume (mL) of Blood to be Drawn from Participants in All Cohorts

Assessment/Procedure	Study Visit				Total
	Screening	CCI			
CBC[a]	0.5		0.5	0.5	1.5 mL
Chemistry Panel[a]	0.5		0.5	0.5	1.5 mL
PK Blood sample	NA		2× 0.3	1 × 0.3	0.9mL
Total	1.0 mL		1.6 mL	1.3 mL	3.9mL

a. Estimated volumes provided for local safety labs, CBC and chemistry panel.

Local laboratories are to be used for this study. 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. In addition, Investigators must identify and record their local laboratory method for analysis of Screat (eg,a non-isotope dilution mass spectrometry (IDMS) traceable method; an enzymatic assay, or IDMS traceable assay to assess Screat in the CRF.

Protocol-specified safety laboratory evaluations may be conducted at a local laboratory as specified in the SoA and can be collected at home, if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital.

If local labs are used, sites must be aware of the IRB/EC recommendations on blood volumes and provide appropriate training to the sites.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Not Applicable

8.3.5. Medically Attended Visits

RSV related medical visits a participant has attended since the last assessment will be collected. Medical visits include those provided by an HCP: outpatient or inpatient visit, emergency room or urgent care visit.

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

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

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

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

During the active collection period as described in Section 8.4.1, each participant's parent(s)/legal guardian 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 parent(s)/legal guardian provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

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

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

If the parent(s)/legal guardian withdraws the participant from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a parent(s)/legal guardian 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/ PSSA.

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 via PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form /PSSA 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 assent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female 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 routes of exposure, eg, ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by routes of exposure, eg, ingestion, inhalation, or skin contact and 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 the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form/ PSSA and an EDP Supplemental Form *or* via PSSA. 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 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 all possible routes of exposure, eg, ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form *or* via PSSA. 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 *or* via PSSA, 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 is a dose-finding and hence this section is not applicable.

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/PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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 or via PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples (venous collection) of approximately 0.3 mL, to provide a minimum of 0.08 mL of plasma, will be collected for measurement of concentrations of sisunatovir as specified in the SoA in Section 1.3.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

If a participant cannot attend visits, PK samples may be collected via CCI [redacted] to measure sisunatovir concentrations.

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 within 10% of the nominal time relative to dosing (eg, within 36 minutes of a 6-hour sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples collected for analyses of sisunatovir plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR. Residual samples from the PK collection may be used for exploratory molecular and proteomic biomarkers.

Samples collected for measurement of plasma concentrations of sisunatovir will be analyzed using validated analytical methods 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 may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Nasopharyngeal (NP) swabs for biomarker research are required and will be collected from all participants in this study as specified in the SoA in Section 1.3:

- **NP Swab Assessments**
  - A baseline NP swab sample (taken pre-dose) will be used to measure RSV RNA levels by quantitative RT-PCR, viral sequencing and to assess for RSV and other respiratory pathogens. This test will not be used to determine study eligibility. The pathogen panel assessment will be batched for analysis and the result will not be available to the sites for real time clinical management.
  - All NP swab samples will be analyzed to measure RSV RNA levels by quantitative RT-PCR (includes an internal quality control for sample collection) and will be utilized for viral sequencing to evaluate potential genetic viral variants. NP samples will be collected by an HCP during a site/CCI /inpatient visit.
  - CCI [redacted] and if permitted by local regulations. Human genetic analyses will not be performed on the NP samples.
  - Residuals of all NP 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. Genetic analyses will not be performed on these NP swab samples. Participant confidentiality will be maintained.

8.7.1. Pharmacodynamic Biomarkers

Pharmacodynamic biomarker analyses are not evaluated 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

Specified protein research is not included in this study.

8.7.4. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.5. Retained Research Samples for Biomarkers

Retained research samples will not be included in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their parent(s)/legal guardian's, agreement to participate in a clinical study following completion of the informed consent process and randomization.
Full analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of 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 product (sisunatovir / placebo) they actually received.
PK Concentration Population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value can be reported.
PK Parameter Analysis Population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest can be reported.
Biomarker Analysis Population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the measured parameters of interest can be reported.

9.3. Statistical Analyses

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

9.3.1. General Considerations

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

Descriptive statistics for all endpoints will be provided overall and by cohort, age and treatment group, when applicable.

The number of participants screened, enrolled, completing the IMP administration, and completing the study will be summarized. The reason for all discontinuations will be summarized overall and by cohort, age and treatment group.

Baseline demographic and other characteristics will be tabulated and summarized by cohort, age and 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).

In general, for continuous endpoints, descriptive statistics (mean, standard deviation, minimum, and maximum) will be provided. For binary endpoints, the proportion of participants with the event will be summarized overall and by cohort, age and treatment group. For categorical endpoints, the proportion of participants for each category will be summarized overall and by cohort, age, and treatment group.

9.3.2. Primary Endpoint(s)

The primary endpoints are related to safety/tolerability with analysis as described in Section 9.3.5

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

The final population PK model will be used to simulate plasma concentration-time curves for sisunatovir for individuals and to calculate post-hoc estimates of PK parameters (CL/F, C_{max}, C_{min}, AUC and $t_{½}$) by age group.

The plasma concentrations of sisunatovir will be listed and descriptively summarized by nominal PK sampling time, treatment, age group, and cohort. Individual participant and summary profiles (mean and median plots) of the plasma concentrations data will be plotted by treatment, age group using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Data permitting, geometric means of PK parameters estimated from the final population PK model will be summarized descriptively by treatment and age group. 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

Tertiary/Exploratory endpoints may not be reported in the CSR and may be reported separately. Descriptive summaries will be presented, if applicable. Further details will be provided in SAP.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, BP, pulse rate, SPO_2, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory and vital sign abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported. Data on premature birth and social factors collected at screening and during the study will be reported.

9.3.6. Other Analyses

9.3.6.1. Biomarker Assessment

Biomarker data collected during the trial may be retained for future analyses. The results of biomarker analyses (except Viral RNA titres) are not planned to be included in the CSR.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling for dose confirmation prior to opening the next age cohort, business decisions regarding future project planning and/or supporting clinical development.

Data from each cohort of the study may be reported in an interim report should the Sponsor determine an interim report is warranted. All analysis will be descriptive in nature.

9.5. Sample Size Determination

The sample size has been chosen empirically to provide safety and tolerability information and is not based on statistical power calculation. There will be up to three dosing cohorts (cohorts 2 [2A, 2B, 2C, 2D] and 3 [3E, 3F, 3B, 3D] are optional):

- Cohorts 1 and 2:

  A: CCI
  B:
  C:
  D:

- Cohort 3:

  E: CCI
  F:

B: [redacted]

D: [redacted]

[redacted] participants ([redacted] active; [redacted] placebo) are planned for each cohort so that approximately [redacted] evaluable participants [redacted] per cohort) may be randomized into the study. The number randomized may be increased if Sponsor recommends repeating the dose for a cohort (ie, an additional [redacted] active and [redacted] placebo may be enrolled in the same cohort). This totals to approximately a maxim m of 108 evaluable participants ([redacted] in each cohort + [redacted] additional in each cohort if necessary). The sample size for cohorts may be reduced to [redacted] active, [redacted] placebo) if there are enrollment challenges. The minimum number of participants is approximately [redacted] evaluable participants (based on [redacted] participants per Cohort) as Cohorts 2 (2A, 2B, 2C, 2D) and 3 (3E, 3F, 3B, 3D) are optional in the study.

Participants may be replaced at Sponsor discretion for the following reasons: if the participant's parent(s)/legal guardian withdraws consent, if the participant misses any dose before providing the [redacted] sample on Day [redacted] or [redacted] if the participant misses any PK samples, if the IMP is discontinued, if the participant's RSV test results at screening are not confirmed by the central laboratory RSV test result, if participant was exposed to a prohibited concomitant medication or if Day 1 RSV RNA levels by RT-qPCR is less than the lower limit of quantification.

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

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 sub-investigators 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/Assent Process

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited, they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent, parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. The participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable are 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's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent, and as applicable, assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

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, participants -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 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 PK and of safety data, 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 RSV test result, safety labs and assessments such as ECG 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.
- Sites may be closed early if they are unable to continue to enroll participants.

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 Investigator Site File or equivalent.

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 1.3). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 8. Protocol Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Reflex tests for DILI and DIKI
Hemoglobin Hematocrit RBC count Platelet count WBC count (total and differential) Mean cell volume (MCV) Mean cell hemoglobin (MCH) MCH concentration (MCHC)	Urea and creatinine eGFR[a] GGT Calcium Sodium Potassium Chloride AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein Cystatin C	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Albumin (urine) Creatinine (urine) Urine albumin to creatinine ratio (ACR)[b]	**DIKI:** Cystatin C Creatinine eGFR UA Albumin (urine) Creatinine (urine) Urine albumin to creatinine ratio (ACR)[b] **DILI:** Albumin CK, direct and indirect bilirubin, AST, ALT, GGT, LDH, PT/INR, eosinophil (%), and alkaline phosphatase

a. eGFR calculation should be according to local laboratory result provided
b. if only ACR is provided by the lab, albumin (urine) and creatinine (urine) do not need to be collected

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.

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 or via PSSA 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/PSSA 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/PSSA for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form/PSSA to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs 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)* 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/ PSSA and EDP Supplemental Form *or* via PSSA.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form *or* via PSSA, 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 *or* via PSSA.

- 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/ PSSA 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 if intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

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

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

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form/PSSA and in accordance with the SAE reporting requirements.

Follow Up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

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

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case PSSA is down 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: Genetics

Not Applicable

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

The threshold of laboratory abnormalities for a potential Drug-Induced Liver Injury (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:

Parameters for pediatric hepatic dysfunction can be defined as at least 2 of the below:

- Total bilirubin >2 × ULN
- AST >2 × ULN
- ALT >2 × ULN

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, eosinophil (%), 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, including factors outlined in the list below, should be collected as applicable.

- Signs and symptoms of hepatotoxicity (nausea, vomiting, fatigue, jaundice, RUQ pain)
- review of ethanol use and consumption
- acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over the counter medications)
- recreational drug use
- 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
- potential occupational exposure to chemicals
- environmental exposures
- household/living arrangements

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 liver enzyme 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 liver enzyme abnormalities.

The preferred tube is the red top tube for liver transaminases (ALT/AST), bilirubin and alkaline phosphatase. For additional information regarding the proper pediatric tubes for these labs, please contact your central lab.

In certain diseases such as rare diseases (eg, Duchenne Muscular Dystrophy) there could be an adjustment to the liver enzyme parameters to account for the increased baseline of the participant entering the clinical trial. Please note hepatic labs reference ranges may differ for adult and pediatric population, certain diseases and lab performing the test.

For additional information regarding DILI please see Guidance for Industry (fda.gov).

Potential Cases of Drug Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined

below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

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

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

collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.6. Appendix 6: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and post-baseline Screat measurement to estimate kidney function [Screat-based eGFR]. Serum Cystatin C (Scys) is an alternative to Screat as a biomarker of kidney function assessment and has been evaluated as a predictor of AKI across the full age spectrum [14-16]. 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.

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.

PEDIATRICS: Currently, no Screat plus Scys eGFR equations have been universally adopted for pediatrics. Therefore, comparison of baseline Screat and Scys to post-baseline Screat and reflex Scys are utilized to support differentiation of AKI from DICI.

Investigators must identify and record their local laboratory method for analysis of Screat (eg, a non-isotope dilution mass spectrometry (non-IDMS) traceable method; an enzymatic assay, or IDMS traceable assay to assess Screat) in the CRF. The sponsor will calculate renal function based on the Screat assay utilized as specified in Section 10.6.2.

10.6.2. Age-Specific Kidney Function Calculations

Age Group	Method	Creatinine Assay	eGFR Calculation
All ages	Schwartz/Brion	Non-IDMS	k × Height (cm) / Screat
≥ 1 yo	Bedside (updated) Schwartz	Enzymatic or IDMS traceable assay	0.413 × (Ht/sCr)
< 1yo	NA	Enzymatic or IDMS traceable assay	Use serum creatinine reference ranges in Table 9 to assess renal function

K: proportionality constant
Ht in cm; Screat in mg/dL

Table 9. Serum creatinine reference values to assess kidney function in neonates and infants < 1 year of age [17]

Age	Median (Predicted) Creatinine Value	2.5%	10%	90%	97.5%
1 Day	55 umol/L (0.62 mg/dL)	37 umol/L (0.42 mg/dL)	43 umol/L (0.49 mg/dL)	70 umol/L (0.79 mg/dL)	81 umol/L (0.92 mg/dL)
2 Day	47 umol/L (0.53 mg/dL)	32 umol/L (0.36 mg/dL)	36 umol/L (0.41 mg/dL)	60 umol/L (0.68 mg/dL)	69 umol/L (0.78 mg/dL)
3 Day	42 umol/L (0.48 mg/dL)	29 umol/L (0.33 mg/dL)	33 umol/L (0.37 mg/dL)	54 umol/L (0.61 mg/dL)	62 umol/L (0.7 mg/dL)
4 Day	39 umol/L (0.44 mg/dL)	27 umol/L (0.31 mg/dL)	31 umol/L (0.35 mg/dL)	50 umol/L (0.57 mg/dL)	58 umol/L (0.66 mg/dL)
5 Day	37 umol/L (0.42 mg/dL)	25 umol/L (0.28 mg/dL)	29 umol/L (0.33 mg/dL)	48 umol/L (0.54 mg/dL)	55 umol/L (0.62 mg/dL)
6 Day	36 umol/L (0.41 mg/dL)	24 umol/L (0.27 mg/dL)	28 umol/L (0.32 mg/dL)	46 umol/L (0.52 mg/dL)	53 umol/L (0.6 mg/dL)
7 Day	34 umol/L (0.38 mg/dL)	23 umol/L (0.26 mg/dL)	27 umol/L (0.31 mg/dL)	44 umol/L (0.5 mg/dL)	51 umol/L (0.58 mg/dL)
2 Weeks	31 umol/L (0.35 mg/dL)	21 umol/L (0.24 mg/dL)	24 umol/L (0.27 mg/dL)	40 umol/L (0.45 mg/dL)	46 umol/L (0.52 mg/dL)
3 Weeks	28 umol/L (0.32 mg/dL)	19 umol/L (0.21 mg/dL)	22 umol/L (0.25 mg/dL)	36 umol/L (0.41 mg/dL)	41 umol/L (0.46 mg/dL)
4 Weeks	25 umol/L (0.28 mg/dL)	17 umol/L (0.19 mg/dL)	20 umol/L (0.23 mg/dL)	32 umol/L (0.36 mg/dL)	37 umol/L (0.42 mg/dL)
2 Months	22 umol/L (0.25 mg/dL)	15 umol/L (0.17 mg/dL)	17 umol/L (0.19 mg/dL)	29 umol/L (0.33 mg/dL)	33 umol/L (0.37 mg/dL)
3 Months	20 umol/L (0.23 mg/dL)	14 umol/L (0.16 mg/dL)	16 umol/L (0.18 mg/dL)	26 umol/L (0.29 mg/dL)	30 umol/L (0.34 mg/dL)

Table 9. Serum creatinine reference values to assess kidney function in neonates and infants < 1 year of age [17]

Age	Median (Predicted) Creatinine Value	2.5%	10%	90%	97.5%
4 to 6 Months	20 umol/L (0.23 mg/dL)	14 umol/L (0.16 mg/dL)	16 umol/L (0.18 mg/dL)	26 umol/L (0.29 mg/dL)	30 umol/L (0.34 mg/dL)
7 to 9 Months	20 umol/L (0.23 mg/dL)	14 umol/L (0.16 mg/dL)	16 umol/L (0.18 mg/dL)	26 umol/L (0.29 mg/dL)	30 umol/L (0.34 mg/dL)
10-12 Months	21 umol/L (0.24 mg/dL)	15 umol/L (0.17 mg/dL)	17 umol/L (0.19 mg/dL)	27 umol/L (0.31 mg/dL)	32 umol/L (0.36 mg/dL)

Note: The values in mg/dL have been rounded to the second decimal place.

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

10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

The KDIGO produces guidelines regarding kidney diseases prevention or management. For example, in the KDIGO guideline regarding chronic kidney disease, GFR category recommendations are available for reference.

AE grading for decline in kidney function will be according to the modified KDIGO criteria for neonates [18] and KDIGO criteria for infants and children ≥28 days old to <12 years old [19] as indicated below.

Criteria used for Staging	Study Population	Stage 1	Stage 2	Stage 3
Modified KDIGO Criteria	All Ages	(i) ≥0.3 mg/dL Screat increase within 48 hours OR (ii) ≥1.5 to 1.9 times Screat increase from baseline (previous lowest value) within prior 7 days)	2.0-2.9 fold Screat increase from baseline	≥3 fold Screat increase from baseline OR Increase in Screat to ≥4.0 mg/dl (≥353.6 mmol/l OR RRT initiation

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

Special Considerations for Neonatal Populations

Neonates (<1 month of age) first few weeks of life have a serum creatinine value that reflects maternal creatinine levels. In addition, renal maturation in the neonates and infants is greatly impacted by prematurity [20-22].

Monitoring and Discontinuation Criteria for All Cohorts

Potential Criteria	Recommendations
Monitoring Criteria	**Neonates < 28 days old:** (i) Screat increase ⩾0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR (ii) Screat increase ≥1.5 to 1.9 times from baseline (previous lowest value) known or suspected to have occurred within the prior 7 days) **Infants and children ≥ 28 days old and < 12 years old:** (i) Screat increase ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR (ii) Screat increase ≥1.5 times baseline known or suspected to have occurred within the prior 7 days
Discontinuation Criteria	• Two sequential increases in serum creatinine that confirm the above changes over the screening or baseline value as indicated in the monitoring criteria. • Note: If the serum creatinine increases may be caused by an identifiable and reversable reason (eg, concomitant medication), then an additional retest may be allowed after discussion with the medical monitor. After retest, a decision for the subject to continue in the study will be made after discussion with the medical monitor.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
ECG Findings That May Qualify as SAEs
• QTcF prolongation >500 msec.
ECG Findings That Qualify as SAEs
• Change in pattern suggestive of new myocardial infarction. • Sustained ventricular tachyarrhythmias (>30 seconds' duration). • Second- or third-degree AV block requiring pacemaker placement. • Asystolic pauses requiring pacemaker placement. • Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion. • Ventricular fibrillation/flutter. • At the discretion of the investigator, any arrhythmia classified as an adverse experience.
The enumerated list of major events of potential clinical concern 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 to be reported as AEs/SAEs.

10.8. Appendix 8: 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 5 half-lives plus 14 days preceding the first dose of study intervention, and through the end of the treatment period or 5 days after last study drug administration for sensitive CCI [redacted] Additionally, administration of proton pump inhibitors must have ended 5 days prior to randomization and administration of H2 blockers must have ended at least 12 hours prior to randomization. The use of antacids is allowed with staggered dosing (ie, not within 3 hours before or after study drug administration). Any administration of proton pump inhibitors or H2 blockers is prohibited during treatment with sisunatovir.

The Pfizer study team is to be notified of any prohibited medications taken during the treatment period. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the treatment period of 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 [redacted] are prohibited, as these medications may have meaningful CCI [redacted]

CCI [redacted] and therefore CCI [redacted] are also prohibited in this study.

CCI [redacted] may be administered with caution during treatment period.

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

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

Prohibited Concomitant Medications

Drug Category	Drugs
CCI	

Drug Category	Drugs
CCI [redacted]	
Proton Pump Inhibitors	Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole Vonoprazan
H2 Blockers	Cimetidine Famotidine Lafutidine Nizatidine Roxatidine

Medications that interact with sisunatovir that may be used with caution or where a dose adjustment may be required (consult the product label for information)

Drug Category	Drugs
CCI [redacted]	

Drug Category	Drugs
CCI	

10.9. Appendix 9: Country Specific Requirements

10.9.1. Argentina

Per local regulations, maternal serology results during pregnancy, or participant's serology results for HIV, HBV, and HCV must be reviewed and recorded in the source document at screening. If any of these serology results are unavailable, then these must be evaluated for the participant to confirm eligibility for enrollment.

Based on the serological test results, the following exclusion will apply: Evidence that participant is positive for HIV, HBV, or HCV infection based on mother's serology results during pregnancy or the participant's serologies.

10.10. Appendix 10: Protocol Specific Appendices

10.10.1. Appendix 10A: Signs and Symptoms Attributable to RSV

Signs or Symptoms	Determining duration of RSV infection at Enrollment	RSV Signs and Symptoms (Entered in CRF)*
New or worsening nasal congestion	X	X
New or worsening runny nose	X	X
Fever (documented temperature of 100.4 or higher) or subjective fever	X	X
New or worsening cough	X	X
Apnea	X	X
Increased respiratory rate** for age: <2 months: ≥60 bpm 2 to <12 months: ≥50 bpm ≥12 to ≤60 months: ≥40 bpm	X	
SpO_2** <95% on room air	X	
Grunting with expiration	X	X
Nasal flaring	X	X
Retractions	X	X
Wheezing	X	X
Rhonchi	X	X
Rales or crackles	X	X
Reduced ability to feed via usual route for >4-6 hours		X
Dehydration due to respiratory distress requiring IV hydration		X

*If a new or worsening symptom (nasal congestion, runny nose or cough) continue to be present at subsequent visits, this should be documented in the CRF, even if the symptom is not worsening.
**SpO2 and RR will be captured through vital signs collection at the in person visit

10.10.2. Appendix 10B: Background and Social Factors

1. Background Factors: Information on the following will be collected for all participants at Screening Visit.

   - Educational level of parent(s) or legal guardian(s).
   - Exposure of participant to smoke (including tobacco smoke).

- Number of persons in the household ≥18 years of age.
- Number of children <18 years of age in the household and if they attend school/ daycare.
    - Number of children in the household under 60 months of age
    - Number of children in the household ≥60 months)
- Breastfeeding information for infant participant (including whether or not breastfeeding is exclusive)

2. Social Factors: Information on the following will be collected per SoA:

- Childcare/daycare attendance (for participants)
- Number of missed days of work for parent(s) or legal guardian(s) due to the infant participant's illness.

10.10.3. Appendix 10C: Chronology of Procedures (Suggested)

For the procedures below, the following chronology of events are suggested, but can be modified based on investigator discretion and adherence to IMP dosing interval:

- Physical exam
- Body weight/length/head circumference
- Vitals signs including SpO_2
- 12 lead ECG (Screening only)
- Blood draws (See SoA Table 3 for Days [redacted] and [redacted])
- NP swab
- IMP administration

10.10.4. Appendix 10D: Dosing and Palatability Questionnaire (eDiary)

Instructions:

- Questionnaire should be filled out by parent, legal guardian or Healthcare professional.
- Please collect the following information:

Background Information

CCI

[redacted]

CCI

[redacted]

For every dose administration, please answer the following questions:

1. Was the participant able to CCI [redacted]?

☐ YES
☐ NO- CCI [redacted]
☐ NO- [redacted]

*CCI [redacted]
☐ 1
☐ 2
☐ 3

*CCI [redacted]

2. Did administration cause any of the following behaviors within 10 minutes from time of completing dose administration?

☐ CCI
☐
☐

10.11. Appendix 11: Protocol Amendment History

Amendment 3 (27 January 2024)

Overall Rationale for the Amendment: The amendment addresses comments and feedback received from regulatory agencies, and incorporates protocol clarifications, and corrections to identified errors.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Following changes to ECG data and monitoring are made (i) Removed ECG from primary endpoint. (ii) ECG will be performed after screening only as needed per investigator discretion. (iii) Updated ECG from triplicate to single. (iv) Exclusion criteria #5 (#4 in Synopsis), #20 removed (v) Exclusion criteria #22 (#15 in Synopsis) modified to remove the ECG triplicate criteria (vi) Removed language about medications that can CCI in prior and concomitant therapy	The thorough QT study (C5241015) did not identify signal of potential clinical concern (PMAR-EQDD-C524b-Pre-Poc-1664).	Section 1.1 Synopsis, Section 1.3.1 SoA, Section 2.3.1 Risk Assessment, Section 3 Objectives, Endpoints and Estimands, Section 5.2 Exclusion criteria, Section 6.9 Prior and Concomitant Therapy, Section 7.1.3 ECG Changes, Section 8.3.3 Electrocardiograms, Section 9.3.5.1 Electrocardiogram Analyses, Section 10.8 Prohibited Concomitant Medications That May Result in DDI, Section 10.10.3 Appendix 10C: Proposed Chronology of Procedures
Extension of diagnostic testing timeframe allowed for Inclusion Criteria #2 for participants to CCI hours.	To allow RSV diagnostic tests conducted within CCI hours of randomization to be used for evaluation of eligibility, instead of CCI hours for participants > CCI days old and CCI hours for participants CCI .	Section 1.1 Synopsis, Section 1.3.1 SoA (Lab Assessments) and Section 5.1 Inclusion Criteria
Extension of RSV related signs and/or symptoms timeframe allowed for Inclusion Criteria #4 to 7 days for participants > CCI days old.	To allow participants > CCI days old with ongoing signs and/or symptoms of RSV disease up to 7 days to remain eligible for participation. This is aligned with the symptom window allowed for the CCI population (CCI old).	Section 1.1 Synopsis and Section 5.1 Inclusion Criteria
Exclusion criteria #13 on known history of renal failure removed.	Sisunatovir is minimally excreted in urine, with renal impairment not expected to have clinically significant effects on PK.	Section 5.2 Exclusion criteria
Removed requirement to review maternal medications in breastfeeding participants	Based on available data (Drugs and Lactation Database (LactMed®) – National Center for Biotechnology Information Bookshelf [nih.gov]), for drugs that are excreted in breast milk, the relative dose in infants relative to mothers is typically ~1% on a weight-adjusted basis and no greater than 4%	Section 1.3 Schedule of Activities, Section 5.2 Exclusion Criteria, Section 6.9 Prior and Concomitant Therapy and Section 10.8 Appendix 8.

Description of Change	Brief Rationale	Section # and Name
	for any CCI [redacted] that has been assessed. Based on these observations it is unlikely that inducers or inhibitors of CCI [redacted] will reach sufficient concentrations to meaningfully alter the pharmacokinetics of sisunatovir; therefore, Inclusion/Exclusion related to concomitant medications in nursing mothers are being removed.	
Clinical Overview updated and included the thorough QT study (C5241015).	To provide an updated summary of ongoing and completed studies.	Section 2.2.4 Clinical Overview
Non-Substantial modifications		
Optional PK CCI [redacted] and the tertiary PK endpoints by microsampling technique is removed.	Suspected instability of sisunatovir while in liquid whole blood state, during the process of drying the collected CCI [redacted] microsamples (based on assay method development and validation activities) (PACL-3, 20 Sep 2023).	Section 1.1 Synopsis, Section 1.3 Schedule of Activities, Section 3 Objectives, Endpoints and Estimands, Section 8.3.4 Clinical Safety Laboratory Assessments, Section 8.5 Pharmacokinetics
Schema corrected for Cohort 2D age band.	To align with age band for cohort 2D in the protocol.	Section 1.2 Schema
Added Pre-dose PK collections on Day 5 to the SoA.	To align Sections 1.3.1 and 1.3.2.	Section 1.3.1 SoA
Added notes on IMP training in the SoA.	To include the IMP training in the SoA.	Section 1.3.1 SoA
Clarified in the SoA, that the safety laboratory tests on Day [redacted] and/or Day [redacted] do not need to be aligned with PK sample collection.	To provide flexibility in the timing of safety labs and remain within the permitted blood volume limits (Section 8.3.4: Table 10) should the safety labs or blood draw already be done as part of standard of care (PACL-7, 22 Dec 2023).	Section 1.3.1 SoA, Section 1.3.2 Multiple Dose PK Days (For All Cohorts), Section 2.3.1 Risk Assessment, Section 8.1 Administrative and Baseline Procedures, Section 8.3.4 Clinical Safety Laboratory Assessments
Added the following footnote: "Day CCI [redacted] visit can occur in person if need". Updated the following footnote for RSV associated signs and symptoms: "Collected if participant have unplanned in person visit between Day CCI [redacted]".	To provide additional clarification.	Section 1.3.1 SOA
Clarified in the SoA, that the Pre-dose (Screening/Day 1) protocol-specified safety labs do not need to be repeated if performed as part of standard of care within 24 hours prior to first dose on Day 1. This includes labs conducted prior to signing of the ICD and these lab results will be entered in the	To reduce the burden of blood draws on the participant and/or remain within the permitted blood volume limits (Section 8.3.4) should the safety labs already be done as part of standard of care and performed within the time frame specified. (PACL-8, 11 Jan 2024)	Section 1.3.1 SoA, Section 2.3.1 Risk Assessment, Section 8.1 Administrative and Baseline Procedures

Description of Change	Brief Rationale	Section # and Name
CRF for the Screening/Day 1 visit.		
Clarified that the study intervention administration period of CCI can be up to 6 consecutive days CCI	To clarify that the IP administration would be CCI for CCI days if 2 doses administered daily Day 1-Day CCI OR for 6 days if not started with 2 doses on Day 1.	Section 1.1 Synopsis, Section 1.3.1 SoA, Section 6.1 Study Intervention(s) Administered.
Simplified background information for non-clinical sections.	IB is referenced.	Section 2.2.1 Nonclinical Pharmacology, Section 2.2.2 Nonclinical Pharmacokinetics and Metabolism, Section 2.2.3 Nonclinical Safety
Added clarification allowing parents/legal guardian to administer study intervention in an inpatient setting if permitted by local policy.	Enable IP administration by parent or legal guardian in an inpatient setting if permitted by local policy to provide flexibility.	Section 2.3.1 Risk Assessment, Section 6.1.1 Administration
Updated the DDI risk information for sisunatovir.	To reflect the latest information.	Section 4.2 Scientific Rationale for Study Design
Clarifications provided for the age range applicable for cohort 1.	To align with other sections in the protocol (PACL-4, 2 Oct 2023).	Section 4.3; Justification for Dose
Clarifications provided for Table 6 header.	To clarify the age ranges as in the C5241003 (PACL-4, 2 Oct 2023)	Section 4.3; Justification for Dose
Clarification of exclusion #6 (#5 in Synopsis) that for participants with past history of elevated bilirubin due to neonatal hyperbilirubinemia that has resolved, they remain eligible.	To provide clarification that if the condition, neonatal hyperbilirubinemia is resolved with normalized T bili values, then the participant remains eligible (PACL-7, 22 Dec 2023).	Section 1.1, Synopsis, Section 5.2 Exclusion criteria
The timing of dosing for the second dose may be adjusted slightly but should be taken at least 4 hours after, but no later than CCI after the first dose. The remaining doses should be taken every CCI .	To allow the participant to select a convenient CCI dosing schedule.	Section 6.1.1 Administration
Remove Viral load and Biomarker as sensitive data.	Viral load is collected at sparse timepoints as an exploratory endpoint with no expectation to detect differences between the treatment groups. Biomarker data is no longer collected in the study (PACL-2, 8 Sep 2023).	Section 6.4.4 Sensitive Data
Receipt of RSV vaccine by participant's mother will no longer be recorded in the CRF.	CRF capture of RSV vaccine information not needed (PACL-7, 22 Dec2023).	Section 6.9 Prior and Concomitant Therapy
Added duration of check for prohibited concomitant medications.	Clarifications on duration of check for prohibited concomitant medications.	Section 6.9 Prior and Concomitant Therapy

Description of Change	Brief Rationale	Section # and Name
Updated criteria for differentiation of AKI (including DIKI) and DICI	To clarify the Scys threshold values to assist with differentiating AKI (including DIKI) from DICI (PACL-5, 17 Oct 2023).	Section 7.1.1 Potential Cases of Acute Kidney Injury
Updated Section 8.3.2.1 heading to "Blood Pressure and Pulse Rate/ Heart Rate".	For clarification.	Section 8.3.2.1 Blood Pressure and Pulse Rate/ Heart Rate
Updated criteria for Adverse Event Grading for Kidney Safety Laboratory Abnormalities.	To align the AE grading for renal function within the different protocol Sections (7.1.1. Potential Cases of Acute Kidney Injury, Section 10.6; Appendix 6: Kidney Safety Monitoring Guidelines and Table 2 in Reference #19 in Protocol Amendment 2 (KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1-138) (PACL-5, 17 Oct 2023).	Section 10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities
Removed Nasopharyngeal swabs and Viral assessments from Pharmacodynamic Biomarkers and provided additional clarification on NP swabs.	Clarified that pharmacodynamic biomarker analyses are not evaluated in this study (PACL-7, 22 Dec2023).	Section 8.7. Biomarker
Added the following criteria for replacement of participants: "if participant was exposed to a prohibited concomitant medication".	To align with Section 10.8.	Section 1.1. Synopsis, Section 4.1. Overall Design, Section 9.5. Sample Size Determination
Sponsor's contact information MQI has been changed.	The process for contacting a medically qualified individual has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List. The Emergency Contact Card is being replaced by a study information card and will no longer be referenced.	Section 10.1.12. Sponsor's Medically Qualified Individual
Added the following footnote to Appendix 2: If only ACR is provided by the lab, albumin (urine) and creatinine (urine) do not need to be collected.	To provide clarification on data collection for ACR.	Section 10.2 Clinical Laboratory Tests
Removed "Please contact the PedCoE (pedcoe@pfizer.com) and the Hepatic Injury Council for more information" from Section 10.5.	This is not applicable as the Medical Monitor is the contact for this study.	Section 10.5 Appendix 5 Liver Safety: Suggested Actions and Follow-Up Assessments
Modified Appendix 8 medication list to include	Removed duplications and improved format of medication table provided.	Section 10.8 Prohibited Concomitant Medications That May Result in DDI

Description of Change	Brief Rationale	Section # and Name
(ii) The prohibited concomitant medications listed in Appendix 8 should not be taken with sisunatovir for the period of time at least equal to 5 half-lives plus 14 days preceding the first dose of study intervention, and through the end of the treatment period or 5 days after study drug administration for sensitive CCI [redacted] (iii) Additional clarifications on CCI [redacted]		
Added the following footnotes in Appendix 10A: If a new or worsening symptoms (nasal congestion, runny nose or cough) continue to be present at subsequent visits, this should be documented in the CRF, even if the symptom is not worsening. SpO2 and RR will be captured through vital signs collection at the in person visit.	Clarification on collection of specific RSV signs and symptoms on CRF.	Section 10.10.1 Appendix 10A: Signs and Symptoms Attributable to RSV
Several additional minor editorial changes made.	To improve clarity and readability and for maintaining consistency throughout the documents.	Throughout Protocol

Amendment 2 (13 September 2023)

Overall Rationale for the Amendment: The amendment addresses comments and feedback received from regulatory agencies, and incorporates protocol clarifications, and corrections to identified errors.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Exclusion criterion 12 in Section 5.2 criterion 11 in synopsis) updated (i) moved renal failure and renal insufficiency to Exclusion Criteria 13 (ii) added a note that preterm participants (if <35 weeks gestational age must be at least one year post-natal age) with bronchopulmonary dysplasia (chronic lung disease of	Clarification on Exclusion criteria #12	Section 1.1; Synopsis, Section 5.2; Exclusion Criteria

Description of Change	Brief Rationale	Section # and Name
prematurity) remain eligible for enrollment.		
Added clarification on definition of AKI and the differentiation of Acute KidneyInjury from DICI based on age-appropriate, pre-specified definitions of acute kidney injury. Removed eCrCL for monitoring kidney function.	To allow for age appropriate pre-specified definitions of Acute Kidney Injury	Section 7.1.1; Potential Cases of Acute Kidney Injury
Added requirement to capture local laboratory method for analysis of Screat.	To allow for kidney function calculations depending on the type of assay used to assess creatinine.	Section 8.3.4; Clinical Safety Laboratory Assessments, Section 10.6.1; Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury
Following changes made regarding genetic analyses for i) NP swab samples that will be used to measure viral RNA levels "may include genetic analysis as an internal control for the assay". ii) CCI [redacted], "and if permitted by local regulations".	To provide more specifics and clarity on genetic analysis of NP swab and residual NP swab samples.	Section 8.7; Biomarkers
Updated Kidney function calculations.	To allow for age-appropriate kidney function assessment.	Section 10.6.2; Age-Specific Kidney Function Calculations
AE grading for Kidney Safety Laboratory Abnormalities updated to use modified KDIGO criteria for neonates and KDIGO criteria for infants and children ⩾ 28 days old to <12 years old.	To provide updates on age-appropriate AE grading for kidney safety laboratory abnormalities.	Section 10.6.4; 10.6.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities
Monitoring and Discontinuation criteria for kidney function updated.	To define age-appropriate AE monitoring and discontinuation criteria for kidney safety laboratory abnormalities.	Section 10.6.4; 10.6.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities.
For participants in Argentina, added requirement of documentation of maternal	Added local, country (Argentina) requirement of documentation of	Section 5.2. Exclusion Criteria; Section 10.9; Appendix

Description of Change	Brief Rationale	Section # and Name
serology results during pregnancy, or participant's serology results for HIV, HBV, and HCV and if unavailable, testing for the same and exclusion of participant if positive for HIV, HBV, or HCV.	serology testing for mothers of participants, or the participants.	9:Country Specific requirements
Added requirement of Optional CCI collection in participants > CCI old.	Clarified that optional CCI collection is only applicable if participant > CCI old in the protocol.	Section 1.3.1; SoA, 1.3.2; Multiple Dose PK Days (For All Cohorts), Section 8.5; Pharmacokinetics
Updated Clinical Laboratory tests to include eGFR calculation to be per local laboratory. Deleted text as no longer applicable based on the above - "; for example: calculation of estimated kidney function (ie, Schwartz eGFR [children only], or Schwartz eGFR [newborns and infants only] as standard lab safety test for clinical studies)"	To allow for eGFR calculation per local method for safety monitoring	Section 10.2; Appendix 2: Clinical Laboratory tests
Non-Substantial modifications		
Removed duplicate Exclusion Criterion 17: Has received corticosteroids equivalent to prednisone ≥2mg/kg daily for at least 14 consecutive days within 30 days prior to study start.	Criterion already included in Section 1.1; Exclusion Criterion 12 (PACL 1 – 04 August 2023).	Section 1.1; Synopsis.
Replacement of participant at sponsor discretion updated to allow for replacement if Day 1 RSV RNA levels by RT-qPCR is less than the lower limit of quantification.	To allow flexibility to replace participants and evaluate RSV viral load change over time.	Section 1.1; Synopsis, Section 4.1; Overall Design, Section, Section 6.5; Study compliance, Section 7.3; Lost to Follow-up, 9.5; Sample Size Determination
Note added to safety labs: If ET occurs after Day 5 visit, safety labs not required.	To align with no requirement of safety labs after Day 5 for the study.	Section 1.3.1; Table 2 SoA
Note added to PK blood sample : If ET occurs after treatment period, PK sample does not need to be collected.	To clarify PK collection and optional CCI collection for ET visit based on when the visit occurs.	Section 1.3.1; Table 2 SoA

Description of Change	Brief Rationale	Section # and Name
Note in SoA for IMP administration changed from IMP (one dose) to be administered to participant at site on Day 1, Day [CCI] and Day [CCI] To IMP (one dose) to be administered to participant during visit on Day 1, Day [CCI] and Day [CCI]	To align with Table 2 which allows Day [CCI] and Day [CCI] visits to be conducted through the Health Home vendor at the participant's home (PACL 1 – 04 August 2023).	Section 1.3.1; Table 2 SoA
Note for Prior/concomitant treatment(s) added: If participant is breastfeeding, mother's medications should be reviewed.	To minimize DDI risk for participants.	Section 1.3.1; Table 2 SoA
Note in SoA that Safety labs to be reviewed in [CCI] and to be ordered stat if feasible in participants [CCI] old, are: ALT, AST, and T bili.	To clarify the specific chemistry labs indicated	Section 1.3.1; Table 2 SoA
Removed collection of [CCI] for Biomarkers intended for Specified Protein Research.	To minimize participant burden for exploratory research in this young pediatric population (PACL 2 08 Sept 2023).	Section 1.3.1; SoA, Section 8.7; Biomarkers, Section 8.7.3; Specified Protein research, Section 8.3.4; Clinical Safety Laboratory Assessments.
Added the following Mitigation strategies for Cardiovascular safety: Exclusion of participants with history or risk factors for QT prolongation, torsades de pointes or congenital deafness. Exclusion of participants with family history of long QT syndrome or sudden unexplained death. Exclusion of participants taking medications known to prolong the QTc interval within 5 half-lives before dosing or requiring during the dosing period. Exclusion if breast feeding participant's mother has taken within 5 half-lives before dosing or requiring during the	Incorporated study mitigations for possible cardiovascular effects into the Risk Assessment Table.	Section 2.3.1; Table 2 SoA

Description of Change	Brief Rationale	Section # and Name
dosing period medications that [redacted]		
Moved Exclusion criterion information related to renal function from Exclusion criteria #12 to separate Exclusion Criterion #13 and added note with examples of renal anomalies that may remain eligible.	To separate the renal exclusion criteria from other comorbidities for clarity. To provide clarification on renal anomalies that may remain eligible for participation (PACL 2, 08 Sept 2023).	Section 5.2; Exclusion Criteria
Exclusion Criterion #11 in Synopsis and Section 5.2 modified to include CPAP: Evidence of severe respiratory failure requiring invasive mechanical ventilation or ECMO. Note: Participants requiring non-invasive ventilation, including high flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP), remain eligible for the study.	Further clarification on non-invasive ventilation provided	Section 1.1; Synopsis, Section 5.2; Exclusion Criteria
Exclusion Criterion 18 (Protocol Amendment 1), Exclusion criteria 19 in Protocol Amendment 2) corrected from: Has received treatment with ribavirin (oral or inhaled) within 3 days of screening To Has received treatment with ribavirin (oral or inhaled) within 30 days of screening.	This change is made to align with Section 6.9. Prohibited Prior Treatments (PACL 4 August 2023).	Section 5.2; Exclusion Criteria
Prior/Concomitant therapy requirements expanded to mothers of participants in the study who are breast-feeding.	To clarifying that since the prohibited medications are exclusionary for the participant, if the participant is breastfed, the prohibited medications would similarly apply to mothers of breastfed participants (PACL2 to be finalized)	Section 5.2; Exclusion Criteria, Section 6.9; Prior and Concomitant Therapy, Section 10.8; Appendix 8; Prohibited Concomitant medications
Removed Caregiver as the administrator of study intervention	To align with the requirement in Section 6.2 of the protocol that administration of study intervention be done by parent(s)/legal guardian only (PACL 2 08 Sept 2023)	Section 6.1.1; Administration
Edited text to clarify recording of feeding within 30 minutes before and after dosing in eDiary.	To clarify the collection of feeding information.	Section 6.1.1; Administration, Section 6.2.1; Preparation and Dispensing

Description of Change	Brief Rationale	Section # and Name
Clarified the actions for missing dose.		
Exclusion criterion 19 (Protocol Amendment 1), Exclusion criteria 20 in Protocol Amendment 2) changed from: Ensure that no concomitant medications that CCI [redacted] are administered to participants. To Has taken within 5 half-lives before dosing or requires during the dosing period of the study any medication that CCI [redacted] Section 6.9 updated.	Clarified the washout period for medications that CCI [redacted] (PACL 4 August 2023).	Section 5.2; Exclusion Criteria, Section 6.9; Prohibited Prior Treatments
Added the following CRF collection requirement: Screening RSV diagnostic test information done to confirm eligibility should be collected in CRF, if available in source document and this should include type of test (antigen or RT-PCR), date and time of testing,	To allow for collection of RSV diagnostic test information to understand discrepant test results should it occur	Section 8.1; Administrative and Baseline Procedures
Removed "Plasma" from Residual plasma samples from the PK collection may be used for exploratory molecular and proteomic biomarkers	To clarify that the residual samples are blood samples and not plasma	Section 8.5; Pharmacokinetics
Added the following – "Approval was expanded the US in July 2023 where neonates and infants are eligible during their first RSV season, and those <24 months of age remain vulnerable during their second season".	To update prophylactic treatments for RSV	Section 2.2; Background

Description of Change	Brief Rationale	Section # and Name
Additional information included for C5241003: One participant randomized to placebo was not included in any of the analysis populations given the evaluable plasma concentration reported at all time points during the treatment period.	To align with IB	Section 2.2.4; Clinical Overview
Moved Breastfeeding information for infant participant from Social factors to Background Factors.	To clarify that this is required to be collected as a background factor	Section 10.10.2; Appendix 10B (Background and Social factors)
Several additional minor editorial changes made.	To improve clarity and readability and for maintaining consistency throughout the documents.	Throughout Protocol

Amendment 1 (26 June 2023)

Overall Rationale for the Amendment: The protocol was amended to address comments received from the US FDA, incorporate protocol clarifications, and correct identified errors.

Description of Change	Brief Rationale	Section # and Name
	Substantial Modifications	
Changed dosing regimen for CCI from CCI days CCI Aligned language in protocol (including updating the SoAs for Cohort 1D, removing Tables 3, 5 and 13; and modifying schema).	To allow for [redacted] days CCI treatment for Cohort 1D	Section 1.1 (Synopsis), Section 1.2 (Schema), Section 1.3 (SoA), Section 2.2 (Background), Section 4.1 (Overall Design), Section 4.3 (Justification of Dose), Section 6.1 (Study Intervention(s) Administered), Section 7.1 (Discontinuation of Study Intervention), Section 8.3.4 (Clinical Safety Laboratory Assessments), Section 10.10.4 Appendix 10D (Dosing and Palatability Questionnaire (eDiary))
Removed the age requirement of "CCI days old" for Exclusion criterion "Evidence of severe respiratory failure requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO)". Mechanical ventilation clarified as "**invasive**" mechanical ventilation	Per FDA feedback. Further clarifications on mechanical ventilation provided	Section 1.1 (Synopsis), Section 5.2 (Exclusion Criteria)

Description of Change	Brief Rationale	Section # and Name
Note added: Participants requiring non-invasive ventilation, including high flow nasal cannula (HFNC), remain eligible for the study.		
Added new exclusion criterion for CCI [redacted] with intrauterine growth restriction.	Per FDA feedback	Section 1.1 (Synopsis), Section 5.2 (Exclusion Criteria)
Revised causality assessment by qualifying "related" as possibly, probably, or definitely related for the below rules Death of a participant during participation in the study receiving study intervention (sisunatovir) and assessed as **possibly, probably, or definitely** related to study intervention (sisunatovir) by the Investigator(s) and/or Sponsor. Two or more SAEs in the same SOC in the study receiving study intervention (sisunatovir) assessed as **possibly, probably, or definitely** related to study intervention (sisunatovir) by the Investigator(s) and/or Sponsor.	Per FDA feedback	Section 4.1.1 (Dose finding and stopping rules)
Change made from "In the event that there is a safety signal of concern, all randomization **may** be halted by the Sponsor until the E-DMC has completed their review and has recommended that further randomization may continue". To "In the event that there is a safety signal of concern, all randomization **must** be halted by the Sponsor until the E-DMC has completed their review and has recommended	Per FDA feedback	Section 4.1 (Overall Design)

Description of Change	Brief Rationale	Section # and Name
that further randomization may continue"		
Changes made to DDI risk for CCI	DDI risk calculations for CCI using the top dose of CCI mg CCI , is now in the same category as the other CCI	Section 2.2.2 (Nonclinical Pharmacokinetics and Metabolism), Section 4.2 (Scientific Rationale for Study Design), Section 10.8 (Appendix 8 Prohibited Concomitant Medications)
Potential Cases of Acute Kidney Injury updated to make the monitoring and discontinuation criteria clearer	To address FDA feedback	Section 7.1.1, Section 10.2 (Appendix 2), Section 10.6 (Appendix 6)
Changes made to the Risk assessment	To align with IB (May 2023)	Section 2.3 (Benefit/Risk Assessment)
Updates to include C5241003 pediatric study results in RSV LRTI participants.	To include results from the completed study and align with IB (May 2023)	Section 2.2.4 (Clinical Overview)
Changed Tertiary Endpoint for Objective: To describe the viral load in NP samples over time in participants with RSV-LRTI From "Viral load measured via RT-PCR in NP swabs over time (including but not limited to change from baseline at **Day** CCI and proportion of participants with BLOQ at Day CCI To "Viral load measured via RT-qPCR in NP swabs over time (including but not limited to change from baseline at **each sampled visit** and proportion of participants with BLOQ at Day CCI	Per FDA feedback	Section 3 (Objectives, Endpoints, and Estimands)
Added an additional Tertiary Endpoint for Objective 'CCI [redacted] "Viral load in NP swabs and RSV signs and symptoms over time in -participants CCI [redacted]	Per FDA feedback	Section 3 (Objectives , Endpoints, and Estimands)

Description of Change	Brief Rationale	Section # and Name
CCI [redacted]		
Edited text to state that "Additional NP swab samples will be collected per the SoA in Section 1.3, and will be analyzed to measure RSV RNA levels by RT-qPCR. NP samples will be collected by an HCP during a site CCI [redacted] /inpatient visit" Clarified residual NP swab samples may be used for viral sequencing, CCI [redacted] if sufficient samples are available.	Per FDA feedback	Section 8.7 (Biomarkers)
Updated Schedule of Activities to (i) include CCI [redacted] Visits for Day CCI and ET visits (ii) include Site Visits for Day CCI and CCI visits (iii) collect RSV signs and symptoms between Day CCI and CCI if participant has an unplanned visit. (iv) collect NP swab (optional) between Day CCI and CCI if participant has an unplanned visit or an in person visit for the Day CCI visit	To give flexibility to participants and allow for collection of additional NP swabs and RSV signs and symptoms on Day CCI	Section 1.3 (Schedule of Activities)
Updated schema and minimum number of participants to align with the change of Cohort 2D to be optional.	Per FDA feedback	Section 1.1 (Synopsis), Section 1.2 (Schema), Section 4.1 (Overall Design), Section 9.5 (Sample Size Determination)
Updated Appendix to allow for collection of all Signs and Symptoms and not just LRTI Signs and Symptoms post-screening, during the study per SoA	To follow RSV infection and not just LRTI during the study	Section 10.10.1. (Appendix 10A: Signs and Symptoms Attributable to RSV)
Removed CCI [redacted] as a diluent to prepare study intervention	To align with regulatory filing	Section 1.1 (Synopsis), Section 2.3.1 (Risk Assessment), Section 6.1 (Study Intervention(s) Administered)

Description of Change	Brief Rationale	Section # and Name
	Non-Substantial modifications	
Added "at the time of screening" to (i) "CCI and (ii) to footnotes for schema	To ensure cohort assignment is based on age determined at screening and not randomization, if screening and randomization do not occur on the same day as dosing is CCI and weight based.	Section 1.1 (Synopsis), Section 1.2 (Schema)
Biomarker collection method in SoA updated	To include fingerprick for dry blood spot collection if applicable	Section 1.3 (SoA)
Removed CCI dosing from CCI Dosing (CCI)"	To clarify and address FDA feedback that dosing is CCI	Section 1.1 (Synopsis), Section 1.2 (Schema), Section 1.3 (SoA), Section 2.2 (Background), Section 2.3.2 (Benefit Assessment), 4.1 (Overall Design), Section 4.2.3 (Rationale for Comparator), Section 4.3 (Justification for Dose), Section 6.1 (Study Intervention(s) Administered), and Section 8.3.4 (Clinical Safety Laboratory Assessments).
Minimum range CCI (based on CCI participants per cohort) is changed to minimum of CCI evaluable participants (minimum of CCI per cohort).	Minimum number of evaluable participants adjusted based on change in non-optional cohorts from 5 (cohorts 1A, 1B, 1C, 1D, 2D) to 4 (cohorts 1A, 1B, 1C, 1D) and based on minimum number of participants as CCI per cohort.	Section 1.1 (Synopsis), Section 4.1 (Overall Design), Section 9.5 (Sample Size Determination)
Note added to Exclusion criterion on clinically significant ECG #3 (#4 in this amendment) Note: If sinus tachycardia is present, and not worse than expected due to the underlying disease, participant may be considered if it does not interfere with evaluation of response to study intervention, at investigator discretion.	Per FDA feedback, clarification added since many infants with bronchiolitis may have significant tachycardia.	Section 1.1 (Synopsis), Section 5.2 (Exclusion Criteria)
Previously Exclusion criterion #12 (#13 in this amendment) combined with Exclusion criteria #15 and 16.	Further clarification on #12 (#13 in this amendment) provided with examples of immunosuppressive treatments.	Section 1.1 (Synopsis), Section 5.2 (Exclusion Criteria)
Updated the timeframe in Exclusion criterion #19 (#20 in this amendment) from 28 days to CCI days of screening.	Per FDA feedback	Section 1.1 (Synopsis), Section 5.2 Exclusion Criteria), Section 6.9 (Prior and Concomitant Therapy)

Description of Change	Brief Rationale	Section # and Name
Changes to Nonclinical and Clinical safety Section.	Changes made to align with IB (May 2023).	Section 2.2.2 (Nonclinical Pharmacology), Section 2.2.3 (Nonclinical safety), Section 2.2.4 (Clinical overview)
Updated "Time of Study intervention preparation" To "**Start** Time of Study intervention preparation"	Clarification that the time of preparation of the study intervention is the start time	Section 10.10.4. (Appendix 10D: Dosing and Palatability Questionnaire (eDiary)
Removed "CCI " from the Dosing and Palatability Questionnaire.	Only diluent is CCI and hence the question is not needed.	Section 10.10.4. (Appendix 10D: Dosing and Palatability Questionnaire (eDiary)
Added language on CCI sample collection should be done per local rules and regulations	To comply with local rules and regulations	Section 8.5 (Pharmacokinetics)
Several additional minor editorial changes made.	To improve clarity and readability and for maintaining consistency throughout the documents.	Protocol

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
6MP	mercaptopurine
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
ACR	albumin to creatinine ratio
ADL	activity/activities of daily living
ADME	bbsorption distribution metabolism excretion
APD90	action potential duration at 90% repolarization
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
AUC24	AUC from 0-24 hours
AUC12	AUC at 12 hours
AUCinf	AUC from tine 0 extrapolated to infinite time
AUCss	AUC at steady state
AUCtau	AUC over dosing interval
AV	atrioventricular
AxMP	auxiliary medicinal product
BLOQ	below limit of quantification
BP	blood pressure
bpm	beats per minute
Cav1.2	voltage-gated calcium channels
CBC	Complete blood count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	clearance
C_{max}	Maximum drug concentration
$C_{max,ss}$	Maximum drug concentration at steady state
C_{min}	Minimum drug concentration
Conmeds	Concomitant medications
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CSR	clinical study report
Ctrough	trough concentration
Ctrough,ss	trough concentration at steady state
CT	clinical trial
CTIS	Clinical Trial Information System
CV	cardiovascular
CCI [redacted]	
DAIDS	Division of AIDS
DCT	data collection tool
DDI	drug-drug interaction
CCI [redacted]	
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
CCI [redacted]	
DU	dispensable unit
EC	ethics committee
EC90	90% maximal effective concentration
ECG	electrocardiogram or electrocardiography
ECMO	extracorporeal membrane oxygenation
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
eDiary	Electronic diary
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EC	exclusion criterion
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
EMA	European Medicines Agency
EOT	end of treatment
eSAE	electronic serious adverse event
ET	Early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
F	fusion
fa	fraction of dose absorbed
FDA	U.S. Food and Drug Administration
FE	food effect
fg	fraction of dose that escapes intestinal metabolism
FIH	first in human
F/U	follow-up

Abbreviation	Term
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GD	Gestation Day
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
CCI	
HBV	hepatitis B virus
HCP	health care professional; health care provider
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
hERG	human ether-à-go-go-Related Gene
HFNC	high flow nasal cannula
CCI	
HIPAA	Health Insurance Portability and Accountability Act
hIPSC-CM	human-induced pluripotent stem cell-derived cardiomyocytes
HIV	human immunodeficiency virus
HPD	hours post dose
HR	heart rate
Ht	height
HV	healthy volunteer
IB	investigator's brochure
IC50	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IDMS	non-isotope dilution mass spectrometry
IMP	investigational medicinal product
IND	investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	investigational Product Accountability Log
IPM	investigational product manual
IRB	institutional Review Board
IRT	interactive Response Technology
IV	intravenous
K	proportionality constant for Schwartz Equation (kidney function)
KDIGO	kidney disease: improving global outcomes
LDH	Lactate Dehydrogenase
LFT	liver function test
LRTI	lower respiratory tract infection

Abbreviation	Term
CCI	
M4	double hydroxylation metabolite
MAD	multiple ascending dose
CCI	
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MQI	medically qualified individual
MTD	maximum tolerated dose
NA	not applicable
NAV1.5	cardiac sodium channel
NG	nasogastric
NIMP	noninvestigational medicinal product
NMN	1-methylnicotinamide
NOAEL	no observed adverse effect level
NP	nasopharyngeal
NTI	narrow therapeutic index
CCI	
OD	once a day
OTC	over the counter
PACL	protocol administrative change letter
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
CCI	
PI	principle investigator
PK	pharmacokinetic(s)
PMAR	population modeling analysis report
POC	point-of-care
PopPK	population pharmacokinetics
PPI	proton pump inhibitors
PR	pulse rate
PSSA	Pfizer's Serious AE Submission Assistant
PT	prothrombin time
q12h	every 12 hours
QD	once daily
QTc	corrected QT interval
QTcB	QTc Bazett interval
QTcF	QTc Fridericia interval
QTcV	QTc using Van de Water's method
QTL	quality tolerance limit

Abbreviation	Term
qual	qualitative
rBA	relative bioavailability
RBC	red blood cell
RCT	randomized controlled trial
RI	renal impairment
RNA	ribonucleic acid
ROA	route of administration
RR	resting rate
RRT	Renal replacement therapy
RSV	respiratory syncytial virus
RSV CV	RSV challenge virus
RSV F	RSV fusion
RT-PCR	reverse transcription polymerase chain reaction
RT-qPCR	reverse transcription quantitative polymerase chain reaction
RUQ	right upper quadrant
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical Analysis Plan
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SpO2	oxygen saturation
SRSD	single Reference Safety Document
SUSAR	suspected Unexpected Serious Adverse Reaction
t1/2	terminal elimination half life
T bili	total bilirubin
TdP	Torsades de pointes
TEAE	treatment emergent adverse event
TI	therapeutic index
CCI [redacted]	
T_{max}	time it takes to reach maximum concentration, C_{max}
TQT	through QT
UA	urine analysis
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
UTI	urinary tract infection
WBC	white blood cell
WHO	World health Organization
ycAPD90	Yamamoto rate corrected action potential duration at 90% repolarisation

Abbreviation	Term
yo	years old

11. REFERENCES

1. Simoes EAF, Bont L, Manzoni P, et al. Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children. Infect Dis Ther. 2018;7(1):87-120.
2. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340):2047-64.
3. Rha B, Curns AT, Lively JY, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Young Children: 2015-2016. Pediatrics. 2020;146(1):e20193611.
4. Langley JM, Bianco V, Domachowske JB, et al. Incidence of Respiratory Syncytial Virus Lower Respiratory Tract Infections During the First 2 Years of Life: A Prospective Study Across Diverse Global Settings. J Infect Dis. 2022;226(3):374-85.
5. Kim L, Rha B, Abramson JS, et al. Identifying Gaps in Respiratory Syncytial Virus Disease Epidemiology in the United States Prior to the Introduction of Vaccines. Clin Infect Dis. 2017;65(6):1020-25.
6. SYNAGIS (palivizumab). US Prescription Information (USPI); Mar 2014, Gaithersburg, MD: MedImmune, LLC. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103770s5185lbl.pdf. Accessed: 23 Mar 2023.
7. SYNAGIS (palivizumab) SmPC. EPAR product information: EMA. Available from: https://www.ema.europa.eu/en/documents/product-information/synagis-epar-product-information_en.pdf. Accessed: 23 Mar 2023.
8. BEYFORTUS (nirsevimab) SmPC. EPAR product information: EMA. Available from: https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf. Accessed: 13 Apr 2023.
9. FDA. FDA Approves New Drug to Prevent RSV in Babies and Toddlers. 17 Jul 2023. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers. Accessed: 14 Aug 2023.
10. World Health Organization. Newborn Health. Newborn Health in the Western Pacific. Available from: https://www.who.int/westernpacific/health-topics/newborn-health#:~:text=A%20newborn%20infant%2C%20or%20neonate,to%20health%20care%20is%20low. Accessed: 27 Mar 2023.
11. U.S. Department of Health and Human Services NIoH, National Institute of Allergy and Infectious Diseases, Division of AIDS,. Division of AIDS (DAIDS). Table for Grading the Severity of Adult and Pediatric Adverse Events. Jul 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed: 08 Mar 2023.
12. Centers for Disease Control and Prevention. Clinical Growth Charts. Jun 2017. Available from: https://www.cdc.gov/growthcharts/clinical_charts.htm. Accessed: 13 Apr 2022.
13. Centers for Disease Control and Prevention. WHO Growth Standards Are Recommended for Use in the U.S. for Infants and Children 0 to 2 Years of Age. Sep 2010. Available from:

https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts. Accessed: 07 Apr 2023.

14. Nakhjavan-Shahraki B, Yousefifard M, Ataei N, et al. Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and meta-analysis. BMC Nephrol. 2017;18(1):120.
15. Lagos-Arevalo P, Palijan A, Vertullo L, et al. Cystatin C in acute kidney injury diagnosis: early biomarker or alternative to serum creatinine? Pediatr Nephrol. 2015;30(4):665-76.
16. Xu X, Nie S, Xu H, et al. Detecting Neonatal AKI by Serum Cystatin C. J Am Soc Nephrol. 2023;34(7):1253-63.
17. Boer DP, de Rijke YB, Hop WC, et al. Reference values for serum creatinine in children younger than 1 year of age. Pediatr Nephrol. 2010;25(10):2107-13.
18. Zappitelli M, Ambalavanan N, Askenazi DJ, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res. 2017;82(4):569-73.
19. KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1-138.
20. Girardi A, Raschi E, Galletti S, et al. Drug-induced renal injury in neonates: challenges in clinical practice and perspectives in drug development. Expert Opin Drug Metab Toxicol. 2017;13(5):555-65.
21. Muhari-Stark E, Burckart GJ. Glomerular Filtration Rate Estimation Formulas for Pediatric and Neonatal Use. J Pediatr Pharmacol Ther. 2018;23(6):424-31.
22. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal Acute Kidney Injury. Pediatrics. 2015;136(2):e463-73.

Document Approval Record

Document Name:	C5241009 Clinical Protocol Phase 1b_Protocol Amendment 4_11 Mar 2024 Clean
Document Title:	C5241009 Clinical Protocol Phase 1b_Protocol Amendment 4_11 Mar 2024 Clean

Signed By:	Date(GMT)	Signing Capacity
PPD	11-Mar-2024 13:57:06	Final Approval
PPD	11-Mar-2024 18:14:58	Business Line Approver
PPD	12-Mar-2024 14:42:40	Manager Approval