Protocol C5241007

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

Statistical Analysis Plan (SAP)

Version: 2

Date: 08 Nov 2024

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 08 Nov 2024	N/A	study discontinuation with very few participants	Because of early discontinuation and low sample size: • Removed inferential analyses, tertiary/exploratory endpoints, supplementary/sensitivity analyses, subset analyses, multiple imputation for missing data (sections 2.1, 2.2, 2.2.1, 2.2.2.1, 2.2.2.2, 2.2.3, 3.2.1.2, 3.4, 3.4.1, 3.4.2, 3.5, 5.1, 5.1.1, 5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.3, 6.1.1.1, 6.1.1.2, 6.2.1.1.1.1, 6.2.1.1.1.2, 6.2.1.1.2.1, 6.2.1.1.2.2, 6.2.1.1.3.1, 6.2.1.1.3.2, 6.2.1.1.4.1, 6.2.1.1.4.2, 6.2.1.1.5.1, 6.2.1.1.5.2, 6.2.1.2, 6.4, 6.4.1, 6.4.2, 6.4.3, 6.4.4, 6.5, 8, Appendix 1) • Removed detailed PK analysis (sections 3.2.3, 4, 6.2.3) • Removed IAs (sections 5, 5.1, 7.1, 7.2, 8) • Simplified selected safety summaries (sections 3.3.2, 3.3.3, 6.3.1, 6.3.2) Because no usage was observed: • Simplified handling of intercurrent event of rescue medication usage (sections 2.1, 2.2.1, 2.2.2.1, 2.2.2.2, 6.1.1.1, 6.2.1.1.1.1, 6.2.1.1.2.1, 6.2.1.1.3.1, 6.2.1.1.4.1, 6.2.1.1.5.1, Appendix 1)
1 04 Oct 2024	Amendment 1 30 Apr 2024	N/A	N/A

For the entire document, text in italic format represents language copied directly from the protocol.

2. INTRODUCTION

Sisunatovir (PF-07923568…) is a potent inhibitor of RSV F protein mediated fusion that is currently being investigated as a treatment of adults with naturally acquired RSV infection who are at increased risk of developing severe illness.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5241007.

2.1. Modifications to the Analysis Plan Described in the Protocol

This study was discontinued due to business reasons, with very few participants enrolled. There were no safety concerns in the decision to stop the study and no changes to the sponsor's assessment of the risk-benefit profile for participants who received sisunatovir in the study.

The amended SAP will therefore focus on descriptive summaries of the primary and key secondary efficacy endpoints and safety summaries.

In sections 3, 9.1.1.2, and 9.3.3 of the protocol, the LRTI estimands and endpoints are generally mentioned in terms of RSV-related LRTI, eg, nsLRTI-RSV. The SAP modifies these endpoints to analyze all-cause LRTI, regardless of the investigator assessment of RSV-relatedness. The direct and indirect impact of RSV on underlying LRTI disease may be difficult to assess. The criteria for severe LRTI are pre-specified and adding the investigator subjective assessment may be confounding.

2.2. Study Objectives, Endpoints, and Estimands

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

Type	Objective	Endpoint	Estimand
		Primary:	
Efficacy	*To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness*	*Proportion of participants with RSV-related hospitalization or death from any cause through Day 28*	Summary statistics by treatment for *proportions of patients experiencing RSV-related hospitalization or death from any cause through Day 28.*
		Key Secondary:	
Efficacy	*To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness*	*Proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28*	Summary statistics by treatment for *proportions of patients experiencing RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28. A hospital visit of any duration will be included.*
		Proportion of participants with progression of LRTI through Day 10	Summary statistics by treatment for *proportions of patients with progression of LRTI through Day 10 … in the*

			*population of participants who do not have … severe LRTI (*sLRTI*) at randomization.*
		Proportion of participants with development of LRTI through Day 10	Summary statistics by treatment for *proportions of patients who develop* sLRTI or nsLRTI *through Day 10 … in the population of participants who do not have* sLRTI or nsLRTI *at randomization.*
		Proportion of participants with resolution of LRTI at Day 15	Summary statistics by treatment for *proportions of patients with resolution of LRTI at Day 15 … in the population of participants who have* sLRTI or nsLRTI *at randomization.*
		Mean number of days alive and free from hospital stay (hospital-free days) through Day 28	Summary statistics by treatment for *means of number of days alive and free from hospital stay (hospital-free days) through Day 28.*
Other Secondary:			
Efficacy	*To compare the efficacy of sisunatovir to placebo for treatment of RSV among non-hospitalized adults at high risk for severe illness*	*Proportion of participants with progression of LRTI through Day 3, 5, 15, and 28*	Summary statistics by treatment for *proportions of patients with progression of LRTI through Day 3, 5, 15, and 28 … in the population of participants who do not have* sLRTI *at randomization.*
		Proportion of participants with development of LRTI through Day 3, 5, 15, and 28	Summary statistics by treatment for *proportions of patients who develop* sLRTI or nsLRTI *through Day 3, 5, 15, and 28 … in the population of participants who do not have* sLRTI or nsLRTI *at randomization.*
		Proportion of participants with	Summary statistics by treatment for *proportions*

		resolution of LRTI at Day 3, 5, 10, and 28	*of patients with resolution of LRTI at Day 3, 5, 10, and 28 … in the population of participants who have* sLRTI or nsLRTI *at randomization.*
		Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28	Summary statistics by treatment for *proportions of patients with improvement in LRTI status at Day 3, 5, 10, 15, and 28 … in the population of participants who have* sLRTI or nsLRTI *at randomization.*
		Number of RSV related days in hospital through Day 28 *Number of RSV related days in ICU through Day 28*	Summary statistics by treatment for *means of number of RSV related days in hospital and separately, number of RSV related days in ICU, through Day 28.*
		Proportion of participants with a clinical response of Improvement or Resolution at Day 5, 10, 15, and 28	Summary statistics by treatment for *proportions of patients with Improvement or Resolution at Day 5, 10, 15, and 28.*
Efficacy	*To compare NP viral load changes among non-hospitalized adults at high risk for severe illness treated with sisunatovir relative to placebo*	*Proportion of participants with undetectable RSV viral load at each study visit through Day 28* *Change from baseline in RSV viral load at each study visit through Day 28*	Summary statistics by treatment for *proportions of patients with undetectable RSV viral load at each visit through Day 28* Summary statistics by treatment for *means of change from baseline in RSV viral load at each study visit through Day 28.*
Safety	*To describe the safety and tolerability of sisunatovir relative to placebo among non-hospitalized adults at high risk for severe illness*	*Proportion of participants with TEAEs through Day 35* *Proportion of participants with SAEs through Day 35*	*NA*

Pharmacokinetics	*To determine the PK of sisunatovir among non-hospitalized adults at high risk for severe illness*	*Plasma concentrations of sisunatovir at steady state (Day 3 or later)*	*NA*

2.2.1. Primary Estimand

The primary estimand of this study is defined according to the primary objective and is in alignment with the primary endpoint. It includes the following attributes:

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

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

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

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

Population-level summary: summary statistics by treatment.

2.2.2. Secondary Estimands

2.2.2.1. Key Secondary Estimands

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

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

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

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

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

Population-level summary: summary statistics by treatment.

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

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

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

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

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

Population-level summary: summary statistics by treatment.

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

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

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

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

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

Population-level summary: summary statistics by treatment.

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

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

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

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

Intercurrent events: The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or

other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered "not resolved". The intercurrent event of "RSV-related hospitalization" after first dose of study medication will also be considered as LRTI "not resolved".

Population-level summary: summary statistics by treatment.

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

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

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

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

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

Population-level summary: summary statistics by treatment.

2.2.2.2. Other Secondary Estimands

Other secondary estimands that are variations of those described above are defined similarly to those above, with appropriate adaptations, eg, Day of the endpoint.

Additional secondary estimands are defined below.

Improvement in LRTI

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

Endpoint: *Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28.*

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

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

"RSV-related hospitalization" after first dose of study medication will also be considered as LRTI "not improved".

Population-level summary: summary statistics by treatment.

2.3. Study Design

The study was discontinued, with very few participants enrolled, prior to any IA. What follows in this section was the planned study design.

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

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

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

Interim analyses:

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

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

If futility or early efficacy are demonstrated at either of the efficacy IAs, the E-DMC recommendations will be reviewed by the Sponsor Management Committee and a determination will be made regarding continuation or cessation of randomization into the study.

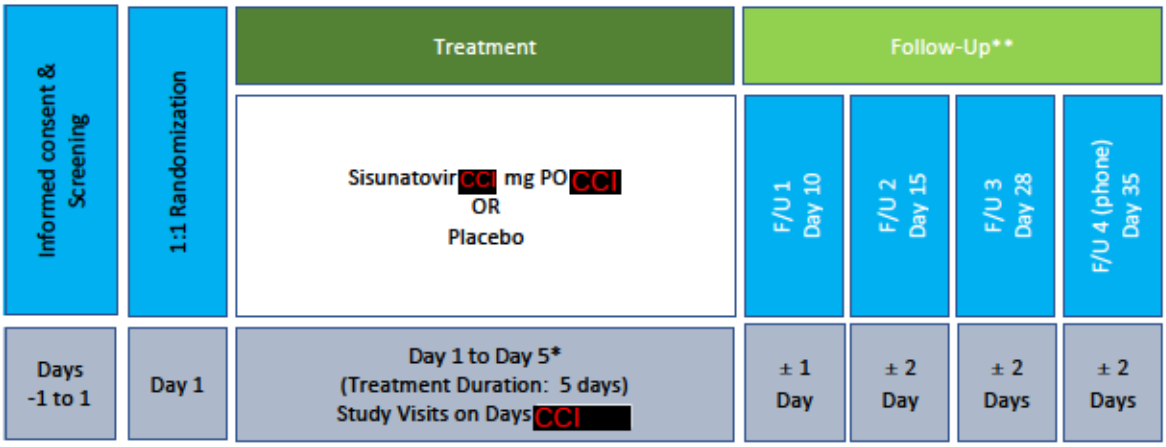
The total study duration for each participant *is up to 5 weeks and includes a screening period of 1-2 days where randomization (Day 1) must occur by the second consecutive day, study intervention administration through Day 5, efficacy outcome assessments through Day 28, and a safety follow-up period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

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

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

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

Figure 1. Study Design



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

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

The primary endpoint is the *proportion of participants with RSV-related hospitalization or death from any cause through Day 28*. It is evaluated in the mITT-infected analysis set.

CCI [redacted] *This includes specialized acute medical care unit within an assisted living facility or nursing home.*

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Key Secondary Endpoints

All key secondary endpoints are evaluated in the mITT-infected analysis set.

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

For this secondary endpoint, no minimum duration of hospitalization is required. If a patient is located in an urgent care or ED at time of randomization, that initial visit would not count towards assessment of this endpoint.

- *Proportion of participants with progression of LRTI through Day 10*

Presence of LRTI is assessed at each clinic visit. If present, the investigator also records on the CRF if it is nsLRTI or sLRTI. This designation is used in LRTI analyses and is not the assessment of intensity grading of the LRTI.

Progression of LRTI is defined as progressing from no LRTI at randomization to nsLRTI or sLRTI*, or from* nsLRTI *at randomization to* sLRTI*, at any time up to and including Day 10.*

- *Proportion of participants with development of LRTI through Day 10*

Development of LRTI is defined as not having LRTI at randomization but having nsLRTI or sLRTI *at any time up to and including Day 10.*

- *Proportion of participants with resolution of LRTI at Day 15*

Resolution of LRTI is defined as having nsLRTI or sLRTI *at randomization and having no LRTI at Day 15.*

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

All hospital days will be counted, regardless of whether or not the hospital admission or hospital day is related to RSV.

3.2.1.2. Other Efficacy-Related Secondary Endpoints

Secondary endpoints in this section are evaluated in the mITT-infected analysis set.

- *Proportion of participants with progression of LRTI through Day 3, 5, 15, and 28*
- *Proportion of participants with development of LRTI through Day 3, 5, 15, and 28*
- *Proportion of participants with resolution of LRTI at Day 3, 5, 10, and 28*
- *Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28*

Improvement in LRTI status is defined as having nsLRTI at randomization and having no LRTI at the Day of interest, or having sLRTI at randomization and having nsLRTI or no LRTI at the Day of interest.

- *Number of RSV related days in hospital through Day 28.*
- *Number of RSV related days in ICU through Day 28.*
- *Proportion of participants with a clinical response of Improvement or Resolution at Day 5, 10, 15, and 28.*
- *Proportion of participants with undetectable RSV viral load at each study visit through Day 28.*

Undetectable RSV viral load at a visit is defined as a central PCR laboratory result of 'TND' (or, a converted numeric value of 0, see below) for both subtype A and subtype B at that visit.

- *Change from baseline in RSV viral load at each study visit through Day 28.*

For numeric viral load summaries, numeric values in units of copies/mL will first be derived from the possible categorical results as follows:

- If the result is 'TND' (target not detected <LOD), a value of CCI will be used, as applicable CCI
- If the result is 'TD' (target detected <LLOQ), CCI
- If the result is CCI Such values may ultimately be replaced by numeric results in subsequent data transfers.

Then for each participant and visit, the total unlogged numeric viral load value will be the sum of the unlogged values, ie, those expressed in units of copies/mL, from subtype A and subtype B. For use in summaries, this total unlogged numeric viral load value will then be transformed to log10 copies/mL, and change from baseline will be calculated from the log10 values. If the sum of the unlogged values is 0, then the transformed value will be set to 0 log10 copies/mL.

See Appendix 2.1 for definition of baseline.

3.2.2. Safety Endpoints

3.2.2.1. Adverse Events

- *Proportion of participants with TEAEs through Day 35.*
- *Proportion of participants with SAEs through Day 35.*

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. An adverse event is considered a TEAE if the event started on or after the study medication start date.

3.2.3. Pharmacokinetic (PK) Endpoints

- *Plasma concentrations of sisunatovir at steady state (Day 3 or later)*

Endpoints planned for all participants will include post-dose samples from Day 3 and pre-dose samples from Day 5, although collection post-dose on Day 5 is allowed if pre-dose collection is not possible.

3.3. Other Safety Endpoints

Other safety endpoints include AEs, laboratory assessments, and vital signs.

Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) will be used for the analysis of standard safety data.

3.3.1. Adverse Event Data

Intensity of TEAEs and relatedness of TEAEs to study drug will be assessed, as well as AEs that lead to discontinuation of study drug and/or study.

3.3.2. Laboratory Data

To determine if there are any clinically significant laboratory abnormalities, the hematological and clinical biochemistry and other safety tests will be assessed against the criteria specified in the Pfizer reporting standards.

3.3.3. Vital Signs Data

Vital signs measures include temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation level. Assessments of potentially clinically important values will be made.

See Appendix 2.1 for definition of baseline.

3.4. Tertiary/Exploratory Endpoints

No tertiary/exploratory endpoints will be summarized for the abbreviated CSR.

3.5. Baseline Variables

Baseline risk factors include:

- age ≥ 65 years
- chronic lung disease
- heart failure
- immunosuppressed (includes immunosuppressive disease or condition, or use of at least 1 specific immune-weakening medication; this is indicated on the Pre-Specified

Significant Medical History – Risk Factors CRF with a response of 'YES' for the 'IMMUNOCOMPROMISED' term).

For laboratory assessments, vital signs, and LRTI assessments, the baseline window will be Day -2 to Day 1, without any consideration to exact time of assessment.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant, or their legally authorized representative, agreed to participate in this clinical study following completion of the informed consent process and the participant was randomized to study intervention.*
Full analysis set	*All participants randomly assigned to study intervention.*
Safety analysis set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they received.* Participants who receive at least 1 dose of sisunatovir will be included in the sisunatovir treatment group.
PK concentration population	*All participants who received at least 1 dose of sisunatovir and in whom at least 1 concentration value can be reported.*

Defined Analysis Set	***Description***
Modified Intent-to-Treat-Infected (mITT-infected)	*All participants randomly assigned to study intervention, who take at least 1 dose of study intervention, and who have* CCI [redacted] *randomization that is defined as* CCI [redacted] *Participants will be analyzed according to the study intervention to which they were randomized.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The study was discontinued, with very few participants enrolled. No inferential testing will be performed.

5.2. General Methods

*Quantitative variables will be described by standard descriptive statistics (*n, *mean, standard deviation,* median, *minimum, and maximum), and qualitative variables will be summarized by frequency tables with number and* percentage *in each category (with the corresponding sample sizes).*

Summaries will be provided *by treatment group and visit (as applicable).*

5.3. Methods to Manage Missing Data

For safety data, missing and partial dates will be programmatically handled according to Pfizer standards.

In all PK data presentations (except listings), concentrations below the limit of quantification (BLOQ) will be set to zero. In listings, BLOQ values will be reported as "<LLOQ", where LLOQ will be replaced with the value for the LLOQ. For PK summary tables, statistics will be calculated having set concentrations to missing if a concentration has been collected as ND (ie, not done) or NS (ie, no sample).

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. RSV-related Hospitalization or Death from Any Cause through Day 28

The primary endpoint is the [p]*roportion of participants with RSV-related hospitalization or death from any cause through Day 28.*

CCI [redacted] *This includes specialized acute medical care unit within an assisted living facility or nursing home.*

6.1.1.1. Main Analysis

- Estimand strategy: treatment policy and composite (section 2.2.1).
- Analysis set: mITT-infected (section 4).
- Analysis methodology: Proportion of participants will be summarized (section 5.2).
- Intercurrent events and missing data: *The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death directly into the endpoint.*
- The number of participants with events will be summarized by treatment group. The proportion of participants with events in each treatment group will be presented.

6.2. Secondary Endpoints

6.2.1. Efficacy Endpoints

6.2.1.1. Key Secondary Endpoints

6.2.1.1.1. RSV-Related Visits (Urgent Care/ED/Hospital) or Death from any Cause through Day 28

6.2.1.1.1.1. Main Analysis

- Estimand strategy: treatment policy and composite (section 2.2.2.1).
- Analysis set: mITT-infected (section 4).
- Analysis methodology: Proportion of participants will be summarized (section 5.2).
- Intercurrent events and missing data: *The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death directly into the endpoint.*
- Results will be presented similarly to those for the primary endpoint (section 6.1.1.1).

6.2.1.1.2. Progression of LRTI through Day 10

6.2.1.1.2.1. Main Analysis

- Estimand strategy: treatment policy and composite (section 2.2.2.1).
- Analysis set: mITT-infected (section 4). Participants must *have either no LRTI or only* nsLRTI at randomization.
- Analysis methodology: Proportion of participants will be summarized (section 5.2).
- Intercurrent events and missing data: *The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered progression of LRTI.* The intercurrent event of "RSV-related hospitalization" after first dose of study medication will also be considered progression of LRTI.
- Results will be presented similarly to those for the primary endpoint (section 6.1.1.1).

6.2.1.1.3. Development of LRTI through Day 10

6.2.1.1.3.1. Main Analysis

- Estimand strategy: treatment policy and composite (section 2.2.2.1).

- Analysis set: mITT-infected (section 4). Participants must *have no LRTI* at randomization.
- Analysis methodology: Proportion of participants will be summarized (section 5.2).
- Intercurrent events and missing data: *The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered development of LRTI.* The intercurrent event of "RSV-related hospitalization" after first dose of study medication will also be considered development of LRTI.
- Results will be presented similarly to those for the primary endpoint (section 6.1.1.1).

6.2.1.1.4. Resolution of LRTI at Day 15

6.2.1.1.4.1. Main Analysis

- Estimand strategy: treatment policy and composite (section 2.2.2.1).
- Analysis set: mITT-infected (section 4). Participants must *have either* nsLRTI or sLRTI at randomization.
- Analysis methodology: Proportion of participants will be summarized (section 5.2).
- Intercurrent events and missing data: *The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death into the endpoint, ie, death will be considered "not resolved".* The intercurrent event of "RSV-related hospitalization" after first dose of study medication will also be considered as LRTI "not resolved".
- Results will be presented similarly to those for the primary endpoint (section 6.1.1.1).

6.2.1.1.5. Days Alive and Free from Hospital Stay (Hospital-Free Days) through Day 28

6.2.1.1.5.1. Main Analysis

- Estimand strategy: treatment policy and composite (section 2.2.2.1).
- Analysis set: mITT-infected (section 4).
- Analysis methodology: Mean number of hospital-free days through Day 28 will be summarized (section 5.2).
- Intercurrent events and missing data: *The intercurrent events "discontinuation from or non-compliance to the planned course of treatment," "discontinuation from the study," and "initiation of rescue or other concomitant medications" are addressed by including all*

available data in the analysis regardless of discontinuation, non-compliance, or use of concomitant medications. The composite strategy is followed for the intercurrent event of "death" by incorporating death directly into the endpoint. No imputation for missing data will be performed for participants who discontinue prior to the Day 28 visit; if on the date of discontinuation, the participant is not hospitalized, the remainder of the time until Day 28 will be assumed to be hospital-free.

- The sample size, mean, SD, median, and range for observed number of hospital-free days will be presented by treatment group.

6.2.1.2. Other Efficacy-Related Secondary Endpoints

- *Proportion of participants with progression of LRTI through Day 3, 5, 15, and 28*

These endpoints will be summarized with the same methods as the similar endpoint through Day 10 (section 6.2.1.1.2.1).

- *Proportion of participants with development of LRTI through Day 3, 5, 15, and 28*

These endpoints will be summarized with the same methods as the similar endpoint through Day 10 (section 6.2.1.1.3.1).

- *Proportion of participants with resolution of LRTI at Day 3, 5, 10, and 28*

These endpoints will be summarized with the same methods as the similar endpoint at Day 15 (section 6.2.1.1.4.1).

- *Proportion of participants with improvement in LRTI status at Day 3, 5, 10, 15, and 28*

These endpoints will be summarized with the same methods as the endpoint of resolution of LRTI at Day 15 (section 6.2.1.1.4.1).

- *Number of RSV related days in hospital through Day 28.*

Health resource utilization data will be summarized by treatment group. This will include number of days of RSV related hospital stay through Day 28. The analyses will be done using the mITT-infected population. Descriptive statistics (ie, mean, SD, median, range) will be used to summarize this endpoint. No imputation for missing data will be performed for participants who discontinue or die prior to the Day 28 visit; the count of RSV related hospital days will be truncated at the date of discontinuation or death.

- *Number of RSV related days in ICU through Day 28.*

Health resource utilization data will be summarized by treatment group. This will include number of days of RSV related ICU stay through Day 28. The analyses will be done using the mITT-infected population. Descriptive statistics (ie, mean, SD, median, range) will be used to summarize this endpoint. No imputation for missing data will be performed for participants who discontinue or die prior to the Day 28 visit; the count of RSV related ICU days will be truncated at the date of discontinuation or death.

- *Proportion of participants with a clinical response of Improvement or Resolution at Day 5, 10, 15, and 28.*

These endpoints will be summarized with the same methods as the endpoint of resolution of LRTI at Day 15 (section 6.2.1.1.4.1). The analysis set is the mITT-infected analysis set (section 4).

- *Proportion of participants with undetectable RSV viral load at each study visit through Day 28.*

This endpoint will be summarized at each study visit (Section 5.2). No imputation for missing data will be performed. The summary will be done using the mITT-infected population.

- *Change from baseline in RSV viral load at each study visit through Day 28.*

Participants are excluded from the analysis for reasons of Not Detected, Zero or Missing baseline viral load result, and local (nonvalidated) swabs use. Results from samples collected at non-nasopharyngeal site (like nostril, other or missing) are also excluded, as well as exclusions due to non-validated swab use (only viral load data based on samples collected through validated swab will be used for analyses).

The viral load measured in nasopharyngeal samples over time will be evaluated. The absolute viral load and change from baseline to each visit (Day 3, Day 5, Day 10, Day 15, Day 28) in viral load will be summarized by treatment group with descriptive statistics (n, mean, SD, median, minimum, and maximum). A spaghetti plot of viral load values over time (by visit) will also be produced, differentiating participants from each treatment group. The analyses will be done using the mITT-infected population.

6.2.2. Safety-Related Secondary Endpoints

- *Proportion of participants with TEAEs through Day 35.*

- *Proportion of participants with SAEs through Day 35.*

All adverse events will be coded according to MedDRA. The incidence of TEAEs and SAEs (if any) will be summarized by treatment group, SOC, and PT for the safety analysis set.

6.2.3. Pharmacokinetic Secondary Endpoints

- *Plasma concentrations of sisunatovir at steady state (Day 3 or later)*

The plasma concentrations of sisunatovir will be listed and descriptively summarized by specific PK sampling windows or nominal sampling time as appropriate.

6.3. Other Safety Summaries and Analyses Endpoint(s)

All safety analyses will be performed on the safety population.

Standard summary tables and listings will be generated in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting for the following parameters: adverse events, lab parameters, vital signs, discontinuations from study, discontinuations from treatment, and treatment duration.

6.3.1. Adverse Event Data

The intensity of TEAEs will be summarized by treatment group, SOC, and PT for the safety analysis set.

6.3.2. Laboratory Data

All laboratory data will be reported in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting.

6.3.3. Vital Signs Data

All vital sign data will be descriptively summarized by treatment group within the safety analysis set and reported in accordance with the Pfizer Data Standards for safety reporting.

6.4. Tertiary/Exploratory Endpoints

No tertiary/exploratory endpoints will be summarized for the abbreviated CSR.

6.5. Subset Analyses

No subset analyses will be performed for the abbreviated CSR.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Baseline demographic and other characteristics will be tabulated for the FAS and summarized by treatment group. This will include age, sex, race, ethnicity, weight, height, BMI, geographic region, presence/absence of specific risk factors, and number of risk factors.

The levels of geographic region will be as follows:

CCI

All baseline disease characteristics will be summarized by treatment group for the FAS. This will include symptom duration, number of days since diagnosis (start date of study treatment – date of diagnosis + 1 [if participant is randomized but not treated, randomization date will be used in place of start date of study treatment]), presence/absence of individual signs/symptoms (from the Signs and Symptoms of ARI CRF), and LRTI status (from the LRTI Assessment Details CRF; any LRTI [yes/no]; if yes, intensity grading

[mild/moderate/severe]; meet criteria for Severe LRTI? [yes/no]; RSV-related? [yes/no/unknown]).

Symptom duration is calculated as CCI [redacted]

For viral load data, baseline visit is set up according to study days of Day -2 to Day 1. Only post-dose results that are within 1 hour post start of dosing will be treated as Baseline data.

6.6.2. Study Conduct and Participant Disposition

The number of participants screened, randomized to the double blind treatment phase…, and treated…*will be summarized from the FAS.* The number of participants completing and discontinuing by study phase, as well as the number of participants in each analysis set will be summarized by treatment group. *The reason for all discontinuations will be summarized by treatment group.*

6.6.3. Study Treatment Exposure

Duration of treatment will be summarized within the safety analysis set.

The duration of treatment will be calculated as follows:

date of last dose of study drug - date of first dose of study drug +1.

7. INTERIM ANALYSES

7.1. Introduction

The study was discontinued, with very few subjects enrolled, prior to any planned IAs.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

Not applicable.

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of participants with RSV-related hospitalization or death from any cause through Day 28	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with RSV-related visits (urgent care/ED/hospital) or death from any cause through Day 28	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with progression of LRTI through Day 10	Summary statistics	mITT-infected with no LRTI or only nsLRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with development of LRTI through Day 10	Summary statistics	mITT-infected with no LRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with resolution of LRTI at Day 15	Summary statistics	mITT-infected with nsLRTI or sLRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Mean number of hospital-free days through Day 28	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events.	NA

Proportion of participants with progression of LRTI through each visit	Summary statistics	mITT-infected with no LRTI or only nsLRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with development of LRTI through each visit	Summary statistics	mITT-infected with no LRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with resolution of LRTI at each visit	Summary statistics	mITT-infected with nsLRTI or sLRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Proportion of participants with improvement in LRTI status at each visit	Summary statistics	mITT-infected with nsLRTI or sLRTI at randomization	All data collected will be included regardless of intercurrent events.	NA
Summary of RSV related days in hospital through Day 28	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events. No imputation will be performed for missing data.	NA
Summary of RSV related days in ICU through Day 28	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events. No imputation will be performed for missing data.	NA
Proportion of participants with a clinical response of Improvement or Resolution by visit	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events.	NA

Proportion of participants with undetectable RSV viral load by visit	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events. No imputation will be performed for missing data.	NA
Change from baseline in RSV viral load by visit	Summary statistics	mITT-infected	All data collected will be included regardless of intercurrent events. No imputation will be performed for missing data.	NA

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

The following table defines the visit windows and labels to be used for reporting other than endpoints assessed for an event through Day 28 (those endpoints use a window of Day 1 to Day 28) and PK endpoints (those endpoints use nominal visit):

Visit Label	Definition [Day window]
CCI	

- Labs, Viral load, Vital Signs, and LRTI: Baseline window will be Day -2 to 1 without any consideration to the time factor. The only exception to time is viral load, where baseline is within 1 hour post start of dosing. If both screening and Day 1 visits are collected on the same calendar day, Day 1 will be used.
- If multiple readings fall into the same window on different days, choose the one closer to the target day. If equidistant, then select the later one after the target day. If multiple readings fall into the same window on the same day at study start, pick Day 1 as the nominal visit over screening for baseline. For vital signs, average the readings if they are on the same day within 10 minutes.
- For labs and viral load, if multiple observations without time or at the same time fall on the same day after the windowing logic has been applied, average observations. If different times on the same day, select the later one.
- When data from study Day 4 has an overlap between Day 3 and Day 5 windows, decision made is to assign the window according to the nominal visit. The rule will not be applicable to other study days 2 and 3 for Day 3 window, and days 5 and 6 for Day 5 window.
- If unplanned viral load (or other outcomes) are assessed on Day 4, then it will be assigned to Day 3. If the nominal Day 3 exists and an unplanned Day 4 assessment is obtained, then the nominal Day 3 visit will still be chosen as the record for the Day 3 window.

Appendix 2.2. Endpoint Derivations

See the Analysis and Reporting plan for further details.

Appendix 2.3. Definition of Protocol Deviations That Relate to Statistical Analyses/Populations

Not applicable.

Appendix 3. Data Set Descriptions

See the Analysis and Reporting plan for further details.

Appendix 4. Statistical Methodology Details

Not applicable.

Appendix 5. List of Abbreviations

Abbreviation	Term
AE	adverse event
APAC	Asia/Pacific
ARI	acute respiratory infection
BLOQ	below the limit of quantitation
BMI	body mass index
CCI	[redacted]
CaPS	CDISC and Pfizer Standards
CDISC	Clinical Data Interchange Standards Consortium
CRF	case report form
CSR	clinical study report
ED	emergency department
E-DMC	external data monitoring committee
FAS	full analysis set
F/U	follow-up

Abbreviation	Term
IA	interim analysis
ICU	intensive care unit
LLOQ	lower limit of quantitation
LOD	limit of detection
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A or NA	not applicable
ND	not done
NP	nasopharyngeal
NS	no sample
nsLRTI	non-severe LRTI
nsLRTI-RSV	RSV-related nsLRTI
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PO	per oral
PT	preferred term
CCI	[redacted]
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase PCR
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
sLRTI	severe LRTI
SOC	system organ class
TD	target detected
TEAE	treatment-emergent adverse event
TND	target not detected
UK	United Kingdom

Abbreviation	Term
ULOQ	upper limit of quantitation
US	United States