



STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Randomized, Placebo-controlled Study of the Safety and Efficacy of Obeldesivir to Treat Nonhospitalized Adults With Acute Respiratory Syncytial Virus (RSV) Infection
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL _{cr}	creatinine clearance
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
DILI	drug-induced liver injury
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol (5-dimensions, 5-levels)
ET	early termination
FAS	Full Analysis Set
FAPS	Full Analysis Positive Set
HCPGIS	Health Care Professional Global Impression of Severity
Hb	hemoglobin
HR	hazard ratio
HLT	high-level term
HLGT	high-level group term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
IRT	interactive response technology
IVT	infectious viral titer
LA	laboratory abnormality
LLT	lowest-level term
LOD	limit of detection
LOQ	limit of quantitation
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
LRT	lower respiratory tract
LRTI	lower respiratory tract infection

LS	least squares
MAV	medically attended visit
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
MST	medical search term
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PSQ	Pre-Existing Symptom Questionnaire
PT	preferred term
Q1, Q3	first quartile, third quartile
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire™
RSV	Respiratory Syncytial Virus
RT-qPCR	reverse transcriptase-quantitative polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SI (units)	international system of units
SOC	system organ class
TA	therapeutic area
TCID50	50% tissue culture infectious dose
TEAE	treatment-emergent adverse event
TELA	treatment-emergent laboratory abnormality
TFLs	tables, figures, and listings
ULN	upper limit of normal
ULOD	upper limit of detection
ULOQ	upper limit of quantitation
URT	upper respiratory tract
UTM	universal transport medium
VR	ventricular rate
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC	area under the concentration versus time curve
AUC _{tau}	area under the concentration versus time curve over the dosing interval
AUC _{x-xx}	partial area under the concentration versus time curve from time “x” to time “xx”
C _{max}	maximum observed concentration of drug
C _{trough}	concentration at the end of the dosing interval
t _{1/2}	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-685-6819. The unblinded primary analysis and the unblinded final analysis will be performed after all participants have completed the study.

This SAP is based on the study Protocol Amendment 2 dated 21 October 2024 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after the finalization of this SAP will be documented in the final clinical study report (CSR).

1.1. Study Objectives and Endpoints

Primary Objective(s)	Primary Endpoint(s)
- To evaluate the efficacy of obeldesivir (ODV; GS-5245) in reducing the duration of symptoms in nonhospitalized adult participants with acute RSV infection - To evaluate the safety and tolerability of ODV administered to nonhospitalized adult participants with acute RSV infection	- Time to alleviation of targeted RSV symptoms as measured by Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) through Day 15 - Incidence of treatment-emergent adverse events (AEs) and laboratory abnormalities through Day 29 - Incidence of serious adverse events and AEs leading to study drug discontinuation
Secondary Objective(s)	Secondary Endpoint(s)
- To evaluate the efficacy of ODV in durably alleviating symptoms of RSV - To evaluate the efficacy of ODV in preventing progression of RSV infection to the lower respiratory tract - To evaluate the efficacy of ODV in preventing hospitalization or death from any cause - To evaluate the efficacy of ODV in preventing MAVs or death from any cause - To evaluate the antiviral activity of ODV on RSV nasal swab viral load at Days 3, 5, 7, 10, and 15 - To evaluate the plasma pharmacokinetics (PK) of GS-441524 (metabolite of ODV)	- Time to sustained alleviation of targeted RSV symptoms as measured by RiiQ through Day 15 - Time to RSV-related lower respiratory tract infection through Day 29 - Time to RSV-related hospitalization or all-cause death through Day 29 - Time to RSV-related MAVs or all-cause death through Day 29 - Change from baseline in RSV viral load through Days 3, 5, 7, 10, and 15 - Plasma concentrations and PK parameters AUC_{0-∞}, C_{trough}, and C_{max} of GS-441524, as available

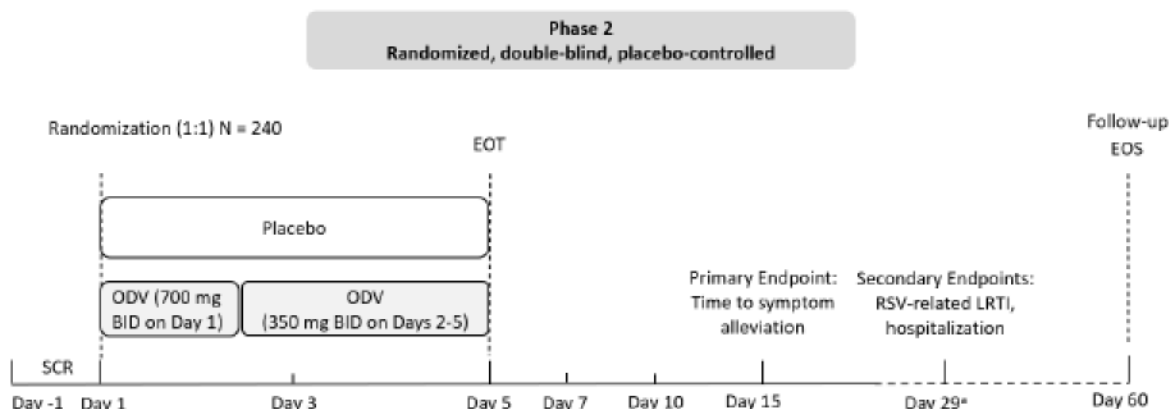
Exploratory Objective(s)	Exploratory Endpoint(s)
- To evaluate the efficacy of ODV in alleviating respiratory and systemic symptoms of RSV - To evaluate the efficacy of ODV in alleviating lower respiratory tract symptoms of RSV - To evaluate the emergence of viral resistance to ODV - To evaluate the efficacy of ODV in improving time to negative RSV nasal swab viral load - To determine the antiviral activity of ODV on RSV nasal swab infectious viral titer - To evaluate the efficacy of ODV in reducing long-term impact of RSV on medical visits, hospitalizations, chronic disease exacerbations, and death from any cause - To evaluate the impact of ODV on prevention of intensive care unit (ICU) admission - To evaluate the impact of ODV on need for noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation - To evaluate the impact of ODV on duration of hospitalization - To evaluate the impact of ODV on health-related quality of life (HRQOL) - To evaluate the impact of ODV on the prevalence of persistent symptoms - To evaluate the efficacy of ODV in treating RSV in participants with respiratory viral coinfection - To evaluate anti-RSV antibodies - To evaluate immune responses secondary to RSV infection and treatment	- Time to alleviation of all RSV symptoms as measured by RiiQ through Day 15 - Time to sustained alleviation of all RSV symptoms as measured by RiiQ through Day 15 - Time to alleviation of lower respiratory tract symptoms of RSV as measured by RiiQ through Day 15 - Emergence of viral resistance to ODV - Proportion of participants with negative RSV nasal swab viral load through Days 3, 5, 7, 10, and 15 - Change from baseline in RSV nasal swab infectious viral titer through Days 3, 5, 7, 10, 15, as applicable - Proportion of participants with negative RSV nasal swab infectious viral titer at Days 3, 5, 7, 10, 15, as applicable - Proportion of participants with all-cause MAVs, hospitalizations, exacerbations of chronic disease (eg, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF]), and all-cause death through Day 60 - Proportion of participants admitted to the ICU through Day 29 - Proportion of participants requiring NIPPV or mechanical ventilation through Day 29 - Hospital length of stay (days) - Change from baseline in EuroQol (5 dimensions, 5 levels) (EQ-5D-5L) at Days 5 and 14 - Duration of persistent symptoms (eg, wheezing or cough) - Symptom duration and virologic response in participants with viral coinfections - Characterization and titer of baseline anti-RSV antibodies - Characterization of cytokine profiles at baseline

1.2. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral ODV with placebo for the treatment of acute RSV infection in nonhospitalized adult participants with ≥ 1 risk factors for severe RSV disease. A total of approximately 240 participants is planned for this study. Central randomization is implemented to minimize bias in the participant treatment assignment. All the enrolled participants are randomized 1:1 to receive ODV (700 mg twice daily on Day 1 followed by 350 mg twice daily on Days 2 to 5) or placebo-to-match for 5 days. Randomization is stratified by vaccination status (ever vs never). Participants will be followed up to 60 days after the first dose of study drug.

An overview of the study design is shown in Figure 1.

Figure 1. Study Scheme



BID = twice daily; EOS = end of study; EOT = end of treatment; LRTI = lower respiratory tract infection; N = number of participants; ODV = obeldesivir (GS-5245); RSV = respiratory syncytial virus; SCR = screening

a At Day 29, an unblinded primary analysis will be conducted and site and participants will remain blinded.

The schedule of study procedures is presented in Appendix 1.

1.3. Sample Size and Power

A total sample size of approximately 240 participants provides at least 80% power to detect a difference of 36 hours (placebo to ODV hazard ratio [HR] 0.7) between ODV over placebo, assuming a median time to symptom alleviation in the placebo group of 5 days (120 hours), and a reduction in median time to symptom alleviation in the ODV group to 3.5 days (84 hours) using a 2-sided significance level of 0.1.

The sample size calculation was performed using software EAST (Version 6.5, module for log-rank test given accrual duration and study duration).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

2.1.1. Planned Internal Analysis

There was 1 planned interim analysis based upon the primary endpoint by the end of the Northern hemisphere RSV season (March 2025) or when approximately 50% of the planned participants have completed Day 29 assessments or prematurely discontinued from the study, whichever occurs first. The analysis was to support program development and planning of Phase 3 studies.

2.2. Primary and Final Analysis

The unblinded primary and final analysis of the primary endpoint will be conducted as one final analysis after all participants have completed the study or prematurely discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint will be conducted at the time of the final analysis and will be tested at the 0.04999 significance level.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by participant ID number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. Participants included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by treatment group and overall.

A listing of participants excluded from any analysis set will be provided.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were randomized in the study.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who took at least 1 dose of study drug.

3.1.3. Full Analysis Positive Set

The Full Analysis Positive Set (FAPS) includes participants in the FAS who are RSV positive at baseline by a central laboratory test. RSV positive is defined as RSV positive at baseline as confirmed by RNA viral load RT-qPCR test and/or multiplex BioFire RP2.1 respiratory pathogen panel test in universal transport medium (UTM) sample. Refer to Appendix 2, Section 14 for the full method description for FAPS determination. Participants missing RSV viral load result in UTM nasal swab sample at baseline will be assumed RSV positive. This is the primary analysis set for efficacy analyses.

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all randomized participants who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.5. Virology Analysis Set

The Virology Analysis Set (VAS) includes all randomized participants who took at least 1 dose of study drug and had a baseline RSV viral load (by RT-qPCR test) greater than or equal to the lower limit of quantitation (LLOQ). Refer to Section 3.7 for the definition of LLOQ.

3.1.5.1. UTM Nasal Swab Virology Analysis Set

The UTM Nasal Swab Virology Analysis Set includes participants in the VAS who had a baseline RSV viral load in UTM nasal swab samples greater than or equal to the LLOQ.

3.1.5.2. Dry Nasal Swab Virology Analysis Set

The Dry Nasal Swab Virology Analysis Set includes participants in the VAS who had a baseline RSV viral load in Dry nasal swab samples greater than or equal to the LLOQ.

3.1.6. Sparse Pharmacokinetic Analysis Set

The Sparse PK Analysis Set will include all randomized participants who received at least 1 dose of study drug and had at least 1 nonmissing sparse PK concentration value reported by the PK laboratory for GS-441524.

3.1.7. Intensive Pharmacokinetic Analysis Sets

3.1.7.1. Intensive Venous Blood Pharmacokinetic Analysis Set

The Intensive Venous Blood PK Analysis Set will include all randomized participants who participated in the optional intensive PK substudy, received at least 1 dose of study drug, and had at least 1 nonmissing intensive PK concentration value from venous blood reported by the PK laboratory for GS-441524.

3.1.7.2. Intensive Capillary Blood Pharmacokinetic Analysis Set

The Intensive Capillary Blood PK Analysis Set will include all randomized participants who participated in the optional intensive PK substudy, received at least 1 dose of study drug, and had at least 1 nonmissing intensive PK concentration value from capillary blood reported by the PK laboratory for GS-441524.

3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set, Full Analysis Set, Full Analysis Positive Set, or Virology Analysis Set, participants will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, sparse PK Analysis Set, or intensive PK Analysis Sets, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Participants will be randomly assigned to treatment groups via the interactive response technology (IRT) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variable:

- Vaccination Status: Ever or Never

If there are discrepancies in stratification factor values between the IRT and the clinical database, the values recorded in the clinical database will be used for analyses. Additionally, stratification discrepancies will be reviewed and assessed. Based on the assessment of stratification discrepancies, a sensitivity analysis of the primary endpoint may be performed.

The primary efficacy endpoint will be evaluated using the stratification factor as covariates or the stratification variable for analyses, as specified in Section 6. If there is an imbalance in presumed prognostic baseline characteristics between treatment groups, efficacy evaluations may be performed that include these baseline values in efficacy analysis models as covariates; these evaluations will be considered sensitivity analyses.

If 5 events or less across both treatment groups are observed within 1 or more stratum, the primary and key secondary endpoints will be evaluated in the same analyses without using the corresponding stratification factor.

3.4. Examination of Participant Subgroups

Subgrouping of participants based on randomization stratification factor will be explored for subgroup analyses. In addition, the primary and select secondary efficacy endpoint(s) will be examined using the following subgroups:

- Age (< 65 years and $\geq$ 65 years)
- Sex (male and female)
- Race: Asian, Black, White, Other

- Risk factors at baseline defined in the main inclusion criteria: age (≥ 60 years vs < 60), chronic obstructive pulmonary disease (COPD), asthma, chronic pulmonary disease, and chronic cardiovascular disease
- RSV subtype at baseline (RSV-A only, RSV-B only)
- RSV viral load in UTM at baseline ($< 6 \log_{10}$ copies/mL and $\geq 6 \log_{10}$ copies/mL)
- Baseline eGFR by CKD-EPI creatinine equation 2021: ≥ 90 mL/min/1.73m², $\geq 60 - < 90$ mL/min/1.73m², $\geq 30 - < 60$ mL/min/1.73m², < 30 mL/min/1.73m²

3.5. Multiple Comparisons

Although this study is not designed to stop early for efficacy based on the interim analysis results, an alpha penalty of 0.00001 based on the Haybittle-Peto {Haybittle 1971} boundary will be applied for the interim analysis.

The primary efficacy endpoint, time to alleviation of targeted RSV symptoms, will be tested at the significance level of 0.04999. There will be no multiplicity adjustment for the secondary efficacy endpoints in this Phase 2 study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

Participants with missing outcomes for the primary endpoint due to premature discontinuation from the study will be censored at the last RiiQ assessment date.

The handling of missing or incomplete dates for AE start is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. Unless specified otherwise, all data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then “15” will be imputed as the day of birth
- If only year of birth is collected, then “01 July” will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at start date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of “< x” (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of “> x” (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.
- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of “≤ x” or “≥ x” (where x is considered the lower or upper LOQ, respectively).

The LLOQ of RSV-A and RSV-B viral load were determined to be 1,000 copies/mL and 250 copies/mL, respectively. The limit of detection (LOD) of the assay for RSV-A and RSV-B were determined to be 620 copies/mL and 80 copies/mL, respectively. The LLOQ of RNase P was determined to be 2,000 Haploid GE/mL. A baseline RSV viral load greater than or equal to the LLOQ refers to either RSV-A $\geq 1,000$ copies/mL or RSV-B ≥ 250 copies/mL. RSV viral load results that are below LLOQ but have a positive signal will be reported as “target detected” and those that are below lower LOD and negative will be reported as “target not detected”. The data will be imputed as follows:

- For RSV-A, a value of 500 copies/mL (half of the LLOQ 1,000 copies/mL) will be used to calculate descriptive statistics if the datum is reported as “target detected”.
- For RSV-B, a value of 125 copies/mL (half of the LLOQ 250 copies/mL) will be used to calculate descriptive statistics if the datum is reported as “target detected”.
- For RSV-A, a value of 310 copies/mL (half of the LOD 620 copies/mL) will be used to calculate descriptive statistics if the datum is reported as “target not detected”.
- For RSV-B, a value of 40 copies/mL (half of the LOD 80 copies/mL) will be used to calculate descriptive statistics if the datum is reported as “target not detected”.

For participants who are classified as RSV-B only at baseline, RSV-A viral load will not be imputed. For participants who are classified as RSV-A only at baseline, RSV-B viral load will not be imputed.

The lower limit of detection (LLOD) and LLOQ are both $1.52 \log_{10}$ TCID₅₀/mL for the infectious viral titer (IVT) assay. The upper limit of detection (ULOD) and upper limit of quantitation (ULOQ) for the IVT assay are $9.04 \log_{10}$ TCID₅₀/mL and $6.35 \log_{10}$ TCID₅₀/mL, respectively. The RSV IVT data will be imputed as follows:

- A value of $0.92 \log_{10}$ TCID₅₀/mL (1/4 of the LLOD $1.52 \log_{10}$ TCID₅₀/mL, after an inverse log transformation) will be used to calculate descriptive statistics if the datum is reported as “ $< 1.52 \log_{10}$ TCID₅₀/mL”. The corresponding qualitative result is “Negative”.
- A value of $9.05 \log_{10}$ TCID₅₀/mL (1 unit above the ULOD) will be used to calculate descriptive statistics if the datum is reported as “ $> 9.04 \log_{10}$ TCID₅₀/mL”. The corresponding qualitative result is “Positive”.
- A value of $6.36 \log_{10}$ TCID₅₀/mL (1 unit above the ULOQ) will be used to calculate descriptive statistics if the datum is reported as “ $> 6.35 \log_{10}$ TCID₅₀/mL”. The corresponding qualitative result is “Positive”.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as “BLQ” in the data listing.

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters in intensive PK samples. Concentration values that are BLQ will be presented as “BLQ” in the concentration data listing. Values that are BLQ will be treated as 0 at predose and one-half of the lower LOQ at postdose time points for summary purposes. The number of samples will be summarized to reflect the actual number of samples assessed at that time point.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the participants have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of order statistics for postdose time points:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as “BLQ”.
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as “BLQ”.
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as “BLQ”.
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as “BLQ”.
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as “BLQ”.

Concentration related PK parameters (eg, C_{last} , C_{max} , and C_{tau}) that are 0 will be excluded before log transformation or statistical model fitting and displayed as described above.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For assessment dates on or after the first dose: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

First Dosing Date is defined as the administration date of the first dose of study drug. If a participant takes the first dose and vomits within 15 mins, then such participant will be re-dosed. In this case, redosing date/time is the official first dosing date/time for the analysis. However, if the participant vomits again, then such participant will be discontinued from the study drug, but still staying in the study.

Last Dose Date is defined as the maximum, nonmissing, nonzero dose end date of treatment recorded on the Study Drug Administration eCRF form with “Study Drug Permanently Withdrawn” box checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF.

Last dose date is not expected to be missing. However, if the last dose date is missing, it will be imputed using the maximum of non-missing, non-zero dose, study drug start and stop dates.

Last Study Date is the latest of the study drug start dates and end dates, the in-person or virtual visit dates, the vital sign collection dates, questionnaire collection dates and the laboratory collection dates, and the death date (if applicable, for participants who died during the study, the death date will be the Last Study Date. For participants who died after completing the study or after prematurely discontinuing the study, the death date will not be considered for the Last Study Date).

Baseline value is defined as the last value obtained on or prior to the first dose date (and time, if available) unless otherwise specified.

3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for the mid-turbinate nasal swab are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for Mid-turbinate Nasal Swab

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4*
Day 5	5	4*	6^
Day 7	7	6^	8 [§]
Day 10	10	8 [§]	12
Day 15	15	13	22
Post Day 15	29	23	36

*If the nominal visit is a scheduled visit and the assessment is done on Day 4 (Study Day = 4), assign to Day 3 or Day 5 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 4, assign to Day 3 analysis window.

^If the nominal visit is a scheduled visit and the assessment is done on Day 6 (Study Day = 6), assign to Day 5 or Day 7 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 6, assign to Day 5 analysis window.

§If the nominal visit is a scheduled visit and the assessment is done on Day 8 (Study Day = 8), assign to Day 7 or Day 10 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 8, assign to Day 7 analysis window.

The analysis windows for laboratory tests are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for chemistry and hematology lab tests

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 5	5	2	10
Day 15	15	11	22
Day 29	29	23	36

RiiQ will be completed daily from predose on Day 1 through Day 29. The Pre-Existing Symptom Questionnaire (PSQ) is only collected predose on Day 1. Windows for RiiQ and PSQ are not assigned, and results for RiiQ will be summarized for each applicable Study Day through Day 29.

The Patient Global Impression of Severity (PGIS) will be completed on Days 1, 3, 15 and 29. The Patient Global Impression of Change (PGIC) will be completed only once on Day 5 (or Day 6) after the final dose, or on ET visit if the last dose occurs prior to Day 5. Window for PGIC is not assigned, and results will be summarized by nominal visit. The Healthcare Professional Global Impression of Severity (HCPGIS) will be completed on Days 1, 3, 5, 15, 29, and the ET visit. The EQ-5D-5L will be completed on Days 1, 5, 15, and 29, and the ET Visit. The analysis windows for PGIS, HCPGIS and EQ-5D-5L are provided in Table 3-3, Table 3-4, Table 3-5, respectively.

Table 3-3. Analysis Visit Windows for PGIS

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	10
Day 15	15	11	22
Day 29	29	23	36

Table 3-4. Analysis Visit Windows for HCPGIS

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4*
Day 5	5	4*	10
Day 15	15	11	22
Day 29	29	23	36

*If the nominal visit is a scheduled visit and the assessment is done on Day 4 (Study Day = 4), assign to Day 3 or Day 5 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 4, assign to Day 3 analysis window.

Table 3-5. Analysis Visit Windows for EQ-5D-5L

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 5	5	2	10
Day 15	15	11	22
Day 29	29	23	36

The analysis windows for vital signs are provided in Table 3-6.

Table 3-6. Analysis Visit Windows for Vital Signs

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 5	5	2	10
Day 15	15	11	22

The analysis windows for urine or serum pregnancy tests are provided in Table 3-7.

Table 3-7. Analysis Visit Windows for Urine or Serum Pregnancy Tests

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 15	15	2	22

Any PK data relating to unscheduled visits will not be assigned to a particular visit or time point and in general will not be included in by-visit summaries but will be included in the listings.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline questionnaire data, the last nonmissing value on or prior to the first dosing date of study drug will be selected. If there are multiple records on or prior to the first dosing date and time, the record prior to and closest to the first dose date and time will be used if available; otherwise, the record after and closest to the first dose date and time will be used.
- For baseline data other than questionnaire, the last nonmissing value on or prior to the first dosing date and time of study drug will be selected, unless specified differently. If there are multiple records on the same day, the baseline value will be selected as follows:
 - For continuous data:
 - For RSV viral load (including two sample category types: UTM Nasal Swab and Dry/Train Nasal Swab) and infectious viral titer data, if there is more than 1 record on the selected day, the latest value will be selected. Within each of viral load sample category types, if there are multiple records with the same time or no time recorded on the same day, the geometric mean value will be taken.
 - For other continuous data, the baseline value will be the average of the measurements.
 - For categorical data:
 - For RSV positivity based on RT-qPCR, multiplex PCR, the worst severity (ie, a positive PCR result) will be selected.
 - For other categorical data, the baseline value will be the measurement with the lowest severity.
- For postbaseline values:
 - The record closest to the nominal day for that visit will be selected.
 - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
 - If there is more than 1 record on the selected day, values will be selected for analysis as follows:
 - For RSV viral load and infectious viral titer, if there is more than 1 record on the selected day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the geometric mean value will be taken.

- For questionnaire data to be summarized, if there is more than 1 record on the selected day, the latest value will be selected.
- For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

If multiple valid, questionnaire language values exist in an analysis window across questionnaires, the primary language will be chosen based on the following rules.

For questionnaire language data to be summarized, if there is more than one language chosen by a participant in the questionnaire, the baseline language value will be selected. If the language chosen in PSQ/RiiQ is different from the language in PGIS, PGIC, HCPGIS, or EQ-5D-5L, then the language reported in PSQ/RiiQ will be the primary language for such participant in the analysis.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (ie, first participant screened, first participant randomized, last participant randomized, last participant last visit for the primary endpoint, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided by treatment group for each investigator within a country, and overall using the All Randomized Analysis Set. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of participants in the stratum will be the total number of enrolled participants. If there are discrepancies in the value used for stratification assignment between the IRT and the clinical database, the value collected in the clinical database will be used for the summary. A listing of participants with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided, if applicable.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of participant disposition will be provided by treatment group and overall. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not randomized with reasons participants not randomized, the number of participants randomized, and the number of participants in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- Full Analysis Positive Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set. In addition, a flowchart will be provided to depict the disposition.

The following by-participant listing will be provided by participant identification (ID) number in ascending order to support the above summary tables:

- Participant disposition, including treatment, date of randomization, first dose date, last dose date, end of study date, study drug discontinuation, study discontinuation, and reasons for study drug or study discontinuation.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure (in days) to study drug will be defined as last dosing date minus first dosing date plus 1.

The total duration of exposure to study drug will be summarized using descriptive statistics. Summaries will be provided by treatment group for the Safety Analysis Set. The presumed total duration of study drug taken by each participant will be determined by the data collected on the study drug administration CRF and maximum days of exposure is 6 days (if the first dose in the afternoon on Day 1).

A by-participant listing of study drug administration and drug accountability will be provided separately by participant ID number (in ascending order).

No formal statistical testing is planned.

4.2.2. Total Number of Tablets Administered

The total number of tablets administered will be summarized using descriptive statistics.

The presumed total number of tablets administered to a participant will be determined by the data collected on the study drug administration CRF using the following formula and maximum tablets administered is 12 tablets:

$$\text{Total Number of Tablets Administered} = \sum \text{No. of Tablets Taken}$$

The imputation rules for missing number of tablets returned are described in programming specifications. Those vomited tablets should be excluded.

4.2.3. Total Number of Administrations

The total number of study drug administrations will be summarized using descriptive statistics. The presumed total number of administrations to a participant will be determined by the data collected on the study drug administration CRF and maximum administration is 10. If a participant takes the first dose and vomits within 15 mins, then such participant will be re-dosed. In this case, redosing is the official first administration. If a participant vomited again after redosing, then the number of administrations is counted as 1.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations will be summarized by treatment group and by deviation category for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with protocol deviations, included a column specify whether the protocol deviation is important.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, age group [≥ 18 - < 65 , ≥ 65 years], sex, race, and ethnicity) and baseline characteristics (body weight, height, body mass index [BMI; in kg/m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set and Full Analysis Positive Set.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data and row mean scores for ordinal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

In addition, similar summaries for the vaccination status (ever versus never) will be provided.

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

The following baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables.

- Randomization stratum: vaccination status (ever versus never)
- Duration of targeted RSV symptoms prior to the first dose of study drug
- Risk factors defined in the inclusion criteria
- Total number of risk factors
- Number of targeted RSV symptoms at baseline measured by RiiQ
- Severity of each targeted RSV symptom as baseline
- Baseline eGFR (by the CKD-EPI creatinine equation in 2021): $\geq 90 \text{ mL}/\text{min}/1.73\text{m}^2$, ≥ 60 - $< 90 \text{ mL}/\text{min}/1.73\text{m}^2$, ≥ 30 - $< 60 \text{ mL}/\text{min}/1.73\text{m}^2$, $< 30 \text{ mL}/\text{min}/1.73\text{m}^2$
- RSV subtype at baseline: RSV-A only, RSV-B only, RSV-A/B Coinfection, and Not Determined

- Baseline RSV viral load in UTM Swabs: combined RSV, RSV-A, and RSV-B (as a continuous variable, and a categorical variable with $< 6 \log_{10}$ copies/mL versus $\geq 6 \log_{10}$ copies/mL)
- Baseline RSV viral load in Dry Swabs and Train Swabs: combined RSV, RSV-A, and RSV-B (as a continuous variable, and a categorical variable with $< 6 \log_{10}$ copies/mL versus $\geq 6 \log_{10}$ copies/mL)
- Baseline respiratory coinfection: None; Yes subdivided into: Influenza A; Influenza B; SARS-CoV-2; Rhinovirus or Enterovirus; Other viral infection; Bacterial infection
- Baseline RSV infectious viral titer (as a continuous variable, and a categorical variable with $< 1.52 \log_{10}$ TCID₅₀/mL versus $\geq 1.52 \log_{10}$ TCID₅₀/mL)
- Ethnicity: Hispanic vs non-Hispanic

The summary of these baseline characteristics will be provided for the Safety Analysis Set and Full Analysis Positive Set. For categorical data, the CMH test (ie, general association statistic for nominal data and row mean scores for ordinal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

A by-participant listing of other baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for general conditions (ie, conditions not specific to the disease being studied). Medical history will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Medical history will be summarized by treatment group and overall by the number and percentage of participants reporting each medical history preferred term. A summary of medical history will be provided for the Safety Analysis Set. No formal statistical testing is planned.

6. EFFICACY ANALYSES

The following two major questionnaires are used to derive planned efficacy endpoints in this study: Respiratory Infection Intensity and Impact Questionnaire (RiiQ), and Pre-Existing Symptom Questionnaire (PSQ).

The RiiQ is a patient-reported outcome measure designed to assess symptoms and impacts of RSV infection. The tool asks respondents to indicate the presence, severity, and impact of 6 symptoms related to the upper and lower respiratory tract (e.g., targeted RSV symptoms) and 7 symptoms related to the systemic responses to infection within the previous 24 hours. The seven systemic symptoms include: headache, feeling feverish, body aches and pains, fatigue, neck pain, interrupted sleep, loss of appetite. Below are corresponding scores, the range for the severity rating and response range for each of the impact scales (e.g., abilities, feelings, and concerns).

Each of the scale scores is done by adding up the responses and dividing by the number of items in each respective scale. If a participant missing below 50% in a scale, the missing value can be replaced by the mean score of the remaining item scores. Otherwise, a score should not be calculated for a participant with over 50% missing items in a scale.

Scores	Severity Rating	Abilities	Feelings	Concerns
0	None	No Difficulty	Not at all	Not at all concerned
1	Mild	Some Difficulty	Somewhat	Somewhat concerned
2	Moderate	Moderate Difficulty	Moderately	Moderately concerned
3	Severe	Great Difficulty	Extremely	Extremely concerned

PSQ assesses the same 13 symptoms as measured in the RiiQ but focuses on symptoms that were present approximately 1 week prior to the development of RSV infection symptoms. The response options range from “None” to “Severe” (scored 0 to 3).

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary endpoint is time (days) to alleviation of targeted RSV symptoms as measured by the Respiratory Infection Intensity and Impact Questionnaire (RiiQ) through Day 15. Alleviation of targeted symptoms is defined as follows:

In participants without any (or with missing) targeted pre-existing respiratory symptoms:

Those targeted symptoms that were not developed or scored mild at baseline should be scored as “None” (score = 0) for 2 consecutive assessments. All targeted symptoms scored moderate or severe at baseline should be scored as “None” (score = 0) or “Mild” (score = 1) for 2 consecutive assessments.

In participants with at least one targeted preexisting respiratory symptom:

- Preexisting targeted symptoms (i.e., present approximately 1 week prior to development of RSV infection symptoms) in the Pre-existing Symptom Questionnaire (PSQ) that were worse (ie, scored higher in RiiQ) at baseline should have improved by at least 1 point on the RiiQ Symptom Scale from baseline for 2 consecutive assessments; and
- Preexisting targeted symptoms that were present in PSQ but not worse (ie, having lower or equal score in RiiQ) at baseline should have not worsened on the RiiQ Symptom Scale from baseline severity for 2 consecutive assessments; and
- Targeted symptoms that were not preexisting at baseline (ie, score = 0 or missing in PSQ) should be scored as “None” (score = 0) or “Mild” (score = 1) on the RiiQ Symptom Scale for 2 consecutive assessments.

The date and time of the first day of the 2 consecutive assessments will be considered the time of symptom alleviation. The date and time stamps at which participants complete the questionnaire each day are captured in electronic diary and will be used to determine whether the requirement of 2 consecutive assessments is satisfied.

Targeted Symptoms are six symptoms related to the upper and lower respiratory tract in the RiiQ listed below:

- Nasal congestion
- Sore throat
- Cough
- Wheezing
- Shortness of breath (dyspnea)
- Expectoration (sputum production)

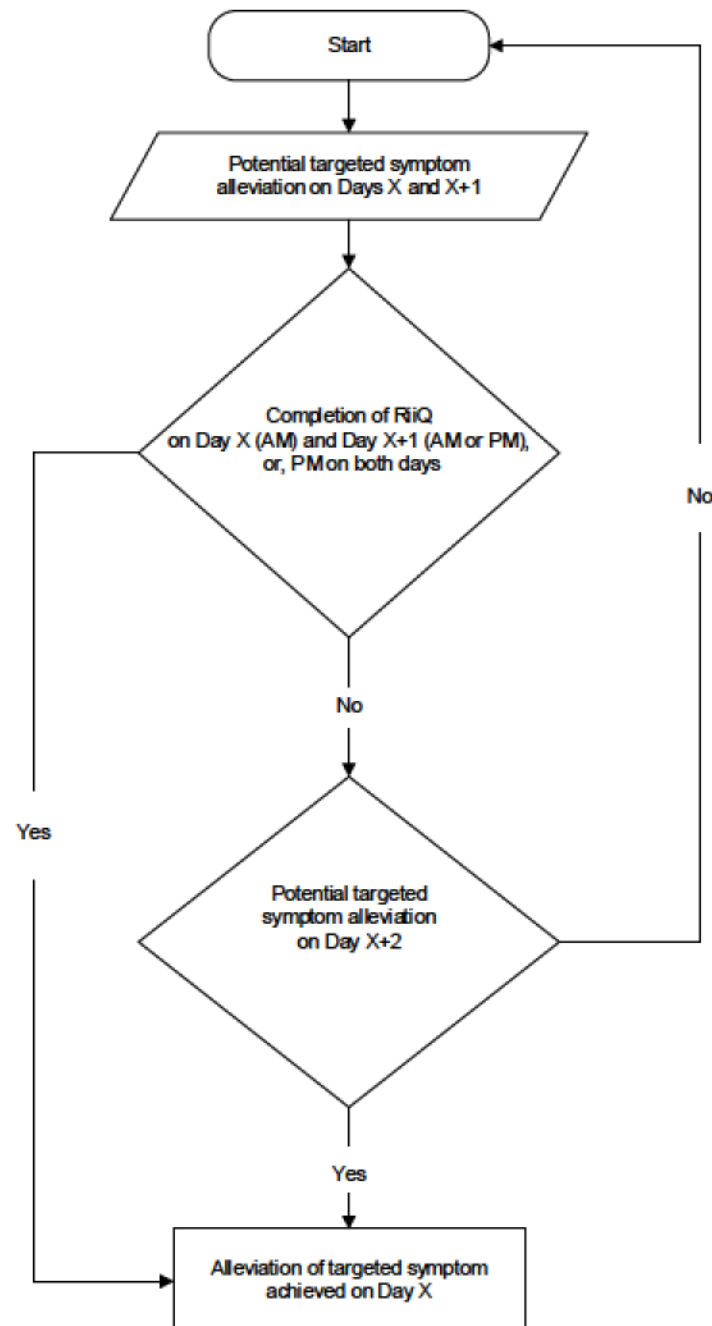
A potential symptom alleviation is identified first and defined as above, ie, without 2 consecutive assessments confirmation. For participants without baseline symptoms, all targeted symptoms need to be scored as none to be considered as potential symptom alleviation.

The AM/PM assessment window for RiiQ on each study day is defined below.

Window	Time Period
AM	00:00:00 - 11:59:59
PM	12:00:00 - 23:59:59

The date-time of the first potential alleviation will be considered as the date-time of symptom alleviation and will be used for the calculation of time to symptom alleviation. Otherwise, repeat the algorithm for the next potential symptom alleviation time.

The determination of two consecutive assessments based on calendar day is shown in the flowchart:



Note: Two consecutive assessments must be on two consecutive calendar days and any missing date in between is not allowed.

Details of algorithms for targeted RSV symptom alleviation are provided in Appendix 2.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: there is no difference in median time (days) to alleviation of targeted RSV symptoms through Day 15 between ODV and placebo.

Alternative hypothesis: there is a difference in median time to alleviation of targeted RSV symptoms through Day 15 between the 2 treatment groups.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

Primary estimand supporting the primary efficacy objective is defined as:

Population: nonhospitalized adult participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease (the study population).

Variable: time to alleviation of targeted RSV symptoms in the absence of rescue medication.

Treatments: ODV and placebo-to-match.

Intercurrent Events: Hospitalization for the treatment of RSV, all-cause death, use of rescue medication, and discontinuation of randomized treatment prior to alleviation of targeted RSV symptoms. Hospitalization for the treatment of RSV or all-cause death means “never achieve alleviation of targeted RSV symptoms” (composite strategy). The use of rescue medication prior to “achieve alleviation of targeted RSV symptoms” means “never achieve alleviation of targeted RSV symptoms” (composite strategy). Discontinuation of randomized treatment will be ignored (treatment policy).

Population Summary: Difference in median time to alleviation of targeted RSV symptoms between ODV and placebo.

The primary estimand is the difference in median time (days) to alleviation of targeted RSV symptoms through Day 15 in the absence of rescue medication or hospitalization for the treatment of RSV between ODV and placebo in adult participants with RSV infection. This will be estimated irrespective of adherence to randomized treatment.

The median time to symptom alleviation and its 95% CI will be estimated by treatment group using the Kaplan-Meier method. A stratified log-rank test with stratification factor included will be used to compare the treatment difference in time to alleviation of RSV symptoms.

Handling of Missing Data and Censoring Rules:

For participants with symptom alleviation by Day 15 (event), time to alleviation of targeted RSV symptom is calculated as symptom alleviation date and time minus the first dose date and time.

- Symptom data missing due to participants prematurely discontinuing from the study or stopping filling out the RiiQ questionnaire. For example, Participants who complete Day 15 of the study or discontinue from the study before Day 15 without alleviation of targeted symptoms will be censored at the last date and time of symptom assessment. The time to alleviation of targeted RSV symptom will be calculated as the last date and time on which the symptom alleviation is assessed by Day 15 minus the first dose date and time or Day 14 whichever occurs first.

- Symptom data missing in certain day(s) but with symptom assessments before and after the missing assessment, symptom alleviation will be considered as “not achieved” on the date with missing symptom data, ie, the two consecutive assessments must be on two consecutive calendar days and any missing date in between is not allowed.
- For participants who experience RSV-related hospitalization, all-cause death, or discontinuation from the study prior to alleviation of symptoms, use of rescue medications prior to alleviation of symptoms will be censored at Day 15.

The proportion of participants with alleviation of targeted RSV symptoms using Kaplan-Meier estimates will be provided in tables and plots by treatment. A Cox proportional hazards regression model will be used to estimate the HR and its 2-sided 95% CI. Stratification factor will be included as a covariate in the Cox proportional hazards model. A sensitivity analysis using a generalized Hodges-Lehmann estimator for the difference in median time to alleviation of RSV symptoms may be performed. The Full Analysis Positive Set (FAPS) will be used for the primary efficacy endpoint analysis.

6.2. Secondary Endpoints

The secondary endpoints include the following:

- Time to Sustained Alleviation of Targeted RSV Symptoms as Measured by RiiQ Through Day 15

Sustained alleviation of targeted RSV symptoms is defined similarly to alleviation of targeted RSV symptoms but for 3 consecutive assessments.

- Time to RSV-related Lower Respiratory Tract Infection (LRTI) Through Day 29

Based on RiiQ, RSV-related LRTI is defined as ≥ 2 of the following symptoms, 1 of which must be reported as at least 'moderate' severity: new or increased cough, new or increased wheezing, new or increased shortness of breath, new or increased expectoration (sputum production), and participant has not met alleviation endpoints.

Note that Nasal congestion and Sore throat are symptoms related to the upper respiratory tract (URT) and Cough, Wheezing, Shortness of breath, and Expectoration are symptoms related to the lower respiratory tract (LRT).

Details of algorithms for these two secondary endpoints are provided in Appendix 2.

- Time to RSV-related Hospitalization or All-cause Death Through Day 29

Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities. RSV relatedness will be determined by the investigator.

- Time to RSV-related Medically Attended Visits or All-cause Death Through Day 29

Medically attended visits are defined as any interactions with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care professional. RSV relatedness will be determined by the investigator.

- Change from baseline in RSV viral load through Days 3, 5, 7, 10, and 15

Respiratory Syncytial Virus (RSV) viral load includes Combined RSV, RSV-A, and RSV-B viral load in midturbinate nasal swab (UTM or Dry) samples.

- Pharmacokinetic parameters AUC_{τ} , C_{trough} , and C_{max} of GS-441524, as available

6.2.1. Secondary Analyses

The estimand for time to sustained alleviation of targeted RSV symptoms through Day 15 is defined as:

Population: nonhospitalized adult participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease (the study population).

Variable: time to sustained alleviation of targeted RSV symptoms in the absence of rescue medication.

Treatments: ODV and placebo-to-match.

Intercurrent Events: Hospitalization for the treatment of RSV, all-cause death, use of rescue medication, and discontinuation of randomized treatment prior to sustained alleviation of targeted RSV symptoms. Hospitalization for the treatment of RSV or all-cause death means “never achieve sustained alleviation of targeted RSV symptoms” (composite strategy). The use of rescue medications prior to “achieve sustained alleviation of targeted RSV symptoms” means “never achieve sustained alleviation of targeted RSV symptoms” (composite strategy). Discontinuation of randomized treatment will be ignored (treatment policy).

Population Summary: Difference in median time to sustained alleviation of targeted RSV symptoms between ODV and placebo.

The estimand for time to sustained alleviation of targeted RSV symptoms through Day 15 is the difference in median time to sustained alleviation of targeted RSV symptoms in the absence of rescue medication or hospitalization for the treatment of RSV between ODV and placebo in the study population. This will be estimated irrespective of adherence to randomized treatment.

The time to sustained alleviation of targeted RSV symptoms through Day 15 will be analyzed in a similar manner to the primary endpoint using the FAPS.

The estimands for time to RSV-related LRTI through Day 29, time to RSV-related hospitalization or all-cause death through Day 29, and time to RSV-related MAVs or all-cause death through Day 29 are defined in Table 6-1 below.

Table 6-1. Estimands for the Other Secondary Efficacy Endpoints

Variable/Follow-Up Time	Time to RSV-related LRTI through Day 29	Time to RSV-related hospitalization or all-cause death through Day 29 Time to RSV-related MAVs or all-cause death through Day 29	Change from baseline in RSV viral load through Days 3, 5, 7, 10 and 15
Population	Nonhospitalized adult participants 18 years of age or older with acute RSV infection and at least 1 risk factor for severe RSV disease		
Treatments	ODV versus placebo-to-match		
Intercurrent Events and corresponding strategies	-		
Hospitalization for the treatment of RSV or all-cause death	Composite strategy means “meeting an RSV-related LRTI” on the date of the intercurrent event(s)	Not Applicable	Treatment policy means ignoring the occurrence of intercurrent events (using observed outcome)
Use of rescue medication		Treatment policy means ignoring the occurrence of intercurrent events (using observed outcome)	Composite policy means considering the occurrence of intercurrent event(s)
Discontinuation of randomized treatment	Treatment policy means ignoring the occurrence of intercurrent events (using observed outcome)		
Population Summary	Hazard ratio, Kaplan-Meier estimates		Least-square (LS) mean difference
Estimator	Estimate hazard ratio from a Cox regression model with stratification factor as a covariate		Estimate difference in LS means from a mixed-effects model repeated measures (MMRM) approach

Variable/Follow-Up Time	Time to RSV-related LRTI through Day 29	Time to RSV-related hospitalization or all-cause death through Day 29 Time to RSV-related MAVs or all-cause death through Day 29	Change from baseline in RSV viral load through Days 3, 5, 7, 10 and 15
Censoring Rules	Participants who complete Day 29 of the study without meeting the endpoint will be censored at Day 29		-
	Participants who discontinue from the study before Day 29 without RSV-related LRTI will be censored at the last assessment of RiiQ	Participants who discontinue from the study before Day 29 without meeting the endpoint will be censored at the last study date	-

Change in RSV viral load from baseline and observed viral load at each postbaseline visit will be summarized. Descriptive statistics will be provided by treatment group as follows:

- Baseline values
- Values at each postbaseline analysis visit
- Change from baseline at each postbaseline analysis visit

The analysis of change in RSV viral load in UTM nasal swab samples will be repeated in subgroups based on baseline RSV subtype (RSV-A, RSV-B), baseline viral load in UTM ($< 6 \log_{10}$ copies/mL, $\geq 6 \log_{10}$ copies/mL), and coinfections (Influenza A, Influenza B, SARS-CoV-2 coinfection, other viral coinfection, and bacterial coinfection). The analysis of RSV viral load in Dry nasal swab samples will be repeated in subgroups based on baseline RSV subtype (RSV-A, RSV-B).

Change from baseline in RSV viral load to each visit will be compared between treatment groups using a mixed-effects model repeated measures (MMRM) approach. The analysis in UTM nasal swab samples will be repeated in subgroups based on baseline viral load ($< 6 \log_{10}$ copies/mL, $\geq 6 \log_{10}$ copies/mL), RSV subtype (RSV-A, RSV-B) at baseline, and coinfections (Influenza A, Influenza B, SARS-CoV-2 coinfection, other viral coinfection, and bacterial coinfection). The analysis in Dry nasal swab samples will be repeated in subgroups based on baseline RSV subtype (RSV-A, RSV-B).

6.3. Exploratory Endpoints

The exploratory endpoints assessed include the following:

- Time to alleviation of lower respiratory tract symptoms of RSV as measured by RiiQ through Day 15.

Alleviation of four lower respiratory tract (LRT) symptoms, including cough, wheezing, shortness of breath, and expectoration, is defined similarly to alleviation of targeted RSV symptoms.

- Time to alleviation of individual targeted RSV symptom through Day 15

The time to alleviation of each of the following LRT symptoms: cough, wheezing, shortness of breath, and expectoration will be provided in plots by treatment group.

- Proportion of participants with negative RSV nasal swab viral load through Days 3, 5, 7, 10, and 15

Negative RSV viral load is defined as a participant with a blank numeric result and “Target Not Detected (TND)”. A numeric result $\geq$ LLOQ, or $<$ LLOQ but “Target Detected” is considered as “Positive”.

- Change from baseline in RSV nasal swab infectious viral titer through Days 3, 5, 7, 10, 15

RSV infectious viral titer (IVT) in mid-turbinate nasal swab samples collected in universal transport medium (UTM) will be analyzed.

- Proportion of participants with negative RSV nasal swab infectious viral titer at Days 3, 5, 7, 10, 15

Negative RSV nasal swab IVT is defined as a participant with a reported result $<$ LLOD. All IVT results $\geq$ LLOD are considered as “Positive”. Participants without baseline IVT data available will not be included in the analysis.

- Proportion of participants with all-cause MAVs, hospitalizations, or all-cause death through Day 60
- Symptom duration and virologic response in participants with viral coinfections

The rest of exploratory endpoints below may be reported separately from the final CSR.

- Time to alleviation of all RSV symptoms as measured by RiiQ through Day 15
- Time to sustained alleviation of all RSV symptoms as measured by RiiQ through Day 15
- Emergence of viral resistance to ODV
- Proportion of participants admitted to the ICU through Day 29
- Proportion of participants requiring NIPPV or mechanical ventilation through Day 29
- Hospital length of stay (days): length of stay will be calculated as end date – start date + 1.
- Change from baseline in EuroQol (5 dimensions, 5 levels) (EQ-5D-5L) at Days 5 and 14
- Duration of persistent symptoms (eg, wheezing or cough)

- PGIS, PGIC, and HCPGIS

The following two exploratory endpoints will be reported in the biomarker analysis report.

- Characterization and titer of baseline anti-RSV antibodies
- Characterization of cytokine profiles at baseline

6.3.1. Analysis of Exploratory Endpoints

The FAPS will be the primary analysis set for exploratory endpoints. The Virology Analysis Set will be the primary analysis set for RSV viral load and infectious viral titer endpoints.

Time to alleviation of lower respiratory tract symptoms of RSV will be analyzed in a similar manner to the secondary efficacy endpoint using the Full Analysis Positive Set (FAPS).

Count and percentage of participants with negative RSV nasal swab viral load will be summarized by treatment group and visit and compared between treatment groups using the Fisher's exact test. The analysis in UTM nasal swab samples will be repeated in subgroups based on baseline viral load in ($< 6 \log_{10}$ copies/mL, $\geq 6 \log_{10}$ copies/mL), RSV subtype (RSV-A, RSV-B) at baseline, and coinfections (Influenza A, Influenza B, SARS-CoV-2 coinfection, other viral coinfection, and bacterial coinfection). The analysis in Dry nasal swab samples will be repeated in subgroups based on baseline RSV subtype (RSV-A, RSV-B).

Analysis of RSV (IVT) includes quantitative and qualitative measurements:

- Quantitative measurements:

Mean infectious viral titer and change in RSV infectious viral titer from baseline at each postbaseline visit will be summarized. Descriptive statistics will be provided by treatment group for change from baseline at each postbaseline analysis visit. The analysis will be repeated in subgroups based on RSV subtype (RSV-A, RSV-B) at baseline.

Change from baseline in RSV infectious viral titer to each visit will be compared between treatment groups using a mixed-effects model repeated measures (MMRM) approach. The analysis will be repeated in subgroups based on RSV subtype (RSV-A, RSV-B) at baseline, if there are enough participants in each subgroup.

- Qualitative measurement:

Count and percentage of participants with negative RSV infectious viral titer will be summarized by treatment group and visit and compared between treatment groups using the Fisher's exact test. The analysis will be repeated in subgroups based on RSV subtype (RSV-A, RSV-B) at baseline.

The proportion of participants with a composite of all-cause MAVs, hospitalizations, or all-cause death by Day 60 in the FAPS will be summarized using Kaplan-Meier estimates and compared between treatment groups using the log-rank test, respectively.

Symptom duration including the time to alleviation of targeted RSV symptoms, the time to sustained alleviation of targeted RSV symptoms, and the time to RSV-related LRTI with viral coinfections at baseline will be summarized separately for each coinfection, including Influenza A, B, SARS-CoV-2, other viral coinfection, and bacteria coinfection, using Kaplan Meier estimates and compared between treatment groups using the log-rank test if there are enough participants in each of the coinfection groups.

The RiiQ will be summarized by overall 13 symptoms, each symptom scale (including systemic symptoms, respiratory symptoms), and each impact scale (including abilities, feelings, and concerns), respectively. In addition, the summary of PSQ score by treatment group will be displayed in a table. Score and change from baseline at each study visit will be compared between treatment groups using a 2-sided Wilcoxon rank-sum test.

6.3.2. Intercurrent Events

Handling of intercurrent events for the exploratory endpoints are shown in Table 6-2. Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements of an endpoint. An event (eg, use of rescue medication) that occurs after an endpoint of interest (eg, symptom alleviation) is not considered as an intercurrent event.

Table 6-2. Handling of Intercurrent Events

Endpoint	Intercurrent event	Strategy	Description
Proportion of participants with all-cause MAVs, hospitalizations, or all-cause death by Day 60	Discontinue randomized treatment prior to endpoint (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
Proportion of participants with exacerbations of chronic disease or all-cause death by Day 60	Use of rescue medication	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)

6.4. Changes From Protocol-Specified Efficacy Analyses

To control the overall type I error, an alpha penalty of 0.00001 is added for the primary analysis. Alpha level for the primary efficacy endpoint at the primary analysis is adjusted accordingly.

7. SAFETY ANALYSES

Analysis of safety data will be conducted on the Safety Analysis Set, unless otherwise specified in the following sections. The treatment-emergent (TE) period is defined as the time period from the first dose date of study treatment up to and including 30 days after the last dose of study treatment.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

<https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf>

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal) according to toxicity criteria specified in document above. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE CRF to the question of “Related to Study Treatment”. Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

Incidence of treatment-emergent adverse events (AEs) and laboratory abnormalities (LAs) through Day 29 and incidence of serious adverse events (SAEs) and AEs leading to study drug discontinuation are the primary safety endpoints of this study.

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as:

- Any AEs with a start date on or after the date of the first dose of study drug and no later than the date of the last dose of study drug plus 30 days.
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the start date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of start determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE start date is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE start date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug.

An AE with completely missing start and stop dates, or with the start date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the start date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE incidence by Severity

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All treatment-emergent deaths observed in the study will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT (if applicable), PT, and treatment group. For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug

Multiple events will be counted only once per participant per treatment in each summary. AEs will be summarized and listed first in alphabetic order of SOC (and HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the worst severity will be used for those AEs that occurred more than once in an individual participant per treatment during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- Treatment-related AEs
- All SAEs
- Treatment-related SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs leading to premature discontinuation of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the date of the last dose of study drug plus 30 days.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, clinical (serum or plasma) chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the DAIDS Grading Scale will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory tests (Hemoglobin, Hematocrit, Platelet Count, White Blood Cells, Red Blood Cells, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin, Serum Creatinine, and estimated glomerular filtration rate (eGFR) as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed change from baseline values for selected laboratory tests will be plotted using a line plot by treatment group and each postbaseline visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (July 2017) will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point during the time period specified in Section 7.2. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities (TELAs)
- Treatment-emergent Grade 3 or 4 laboratory abnormalities (LAs)

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values during the time period specified in Section 7.2.

A by-participant listing of all TELAs and treatment-emergent Grade 3 or 4 LAs will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of participants who were reported to have the following laboratory test values for postbaseline measurements:

- AST: (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 x ULN; (b) > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, participants will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of participants who met at least 1 of the above criteria will be provided.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, height, BMI and vital signs as follows:

- Baseline value
- Values at each postbaseline analysis window visit
- Change from baseline at each postbaseline analysis window visit

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the Gilead-modified World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a participant took the first study drug. Any medication with a start date prior to the first dosing date of study drug is a prior medication regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be prior medications, unless otherwise specified.

A summary of prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each treatment group. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number. No additional safety measures are specified in the protocol.

7.6. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Pharmacokinetic assessments will be conducted in all participants during an in-person visit.

Approximately 30 participants at participating sites will have intensive venous and capillary blood PK samples collected simultaneously. For participants in the optional intensive PK substudy, sparse PK samples will not be collected on the days of intensive PK sampling.

- **Sparse PK assessments**

- Day 1: 0.25, 0.75, and 1.5 hours postdose
- Day 3: predose [< 5 minutes before dosing]
- Day 5: predose [< 5 minutes before dosing] and 0.75 and 2 hours postdose

Note: $\pm 20\%$ time window will be applied for all postdose time points. A single PK sample will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose or at the ET visit for all participants who discontinue the study earlier than Day 10.

- **Intensive PK assessments (venous and capillary blood samples)**

- Day 1: 0.25, 0.5, 0.75, 1.5, 3, 4 hours
- Day 5: predose (< 5 minutes before dose), 0.25, 0.5, 0.75, 1.5, 3, 4 hours after morning or evening dose at the clinic.

Note: $\pm 20\%$ time window will be applied for all postdose time points. Single venous and capillary PK samples will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose or at the ET visit, for all participants who discontinue the study earlier than Day 10.

8.2. PK Analyses Related to Intensive PK Sampling

Pharmacokinetic parameters will be determined for participants in the intensive PK Substudy Analysis Set. Concentrations of GS-441524 in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of PK Parameters

Pharmacokinetic parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up log down rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0. Pre-dose concentration values on Day 5 will also be used as 12-hours postdose values to allow for AUC_{tau} estimation.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the Clinical Pharmacology Study Lead or designee on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the Clinical Pharmacology Study Lead or designee.

8.2.2. PK Parameters

Pharmacokinetic parameters will be generated for all participants in the intensive PK Substudy Analysis Set, as data permits. The analytes, sample type, and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-1. Pharmacokinetic Parameters for Analyte

Analyte	Sample Type	Parameters
GS-441524	Venous	AUC _{tau} , C _{trough} , and C _{max}
GS-441524	Capillary	AUC _{tau} , C _{trough} , and C _{max}

Individual participant concentration data and individual participant PK parameters for GS-441524 will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, geometric mean, 5th percentile, 95th percentile, Q1, and Q3) will be presented for both individual participant concentration data by time point and individual participant PK parameters by treatment. Moreover, the geometric mean, %CV for the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower LOQ at postdose time points.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter.

The following tables will be provided for the analyte of interest by treatment:

- Individual participant concentration data and summary statistics
- Individual participant plasma PK parameters and summary statistics
- Individual participant plasma PK parameters and summary statistics by baseline eGFR categories.

The following figures may be provided for the analyte of interest by treatment:

- Mean ($\pm$ SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are $\leq$ LOQ will not be displayed in the figures and remaining points connected.

Pharmacokinetic sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

Table 8-2. Statistical Comparison for Pharmacokinetic Analysis

Analyte	Parameters	Comparison	
GS-441524	AUC _{tau} , C _{max} , C _{trough}	Capillary sample (Test)	Venous sample (Reference)

For the analyte of interest and PK parameter, a parametric (normal theory) mixed-effects analysis of variance (ANOVA) model with sample source (capillary vs venous) as a fixed effect will be fitted to the natural log-transformed values of the PK parameter under evaluation using SAS[®] PROC MIXED. The following SAS code will provide the comparison analysis and the 90% CI calculations for natural log-transformed PK parameters.


```
proc mixed;  
  where analyte='GS-441524' and param='AUCtau';  
  class subjid sample_source;  
  model lnest = sample_source / ddfm=kr;  
  random subjid;  
  lsmeans source / diff cl alpha = 0.1;  
  estimate 'Test versus Reference' source -1 1 / cl alpha = 0.10;  
  ods output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE;  
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}.

8.3. PK Analyses Related to Sparse PK Sampling

Individual participant concentration data from Participants in the sparse PK Analysis Set for GS-441524 will be listed and summarized using descriptive statistics. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, 5th percentile, 95th percentile, Q1, Q3, geometric mean, %CV, and 95% CI for geometric mean) will be presented by day and by nominal time point.

Due to the sparse nature of PK collection, PK parameters will not be calculated.

Sparse and intensive PK sampling data from this study may be combined with data from other studies in a meta-population analysis using mixed-effect modeling techniques. Details of the population PK analysis will be provided in a separate document.

9. REFERENCES

Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol 1971;44 (526):793-7.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

East® 6.5. Cytel, Waltham, MA, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessments

Study Day		Baseline Day 1 ^{a, c, d}							Day 60 Follow-up Visit	
			Day 3 ^d	Day 5 ^{c, d}	Day 7	Day 10	Day 15 ^c	Day 29		
Visit Window	Screening ^{a, b}		± 1 Day ^e			± 2 Days		+ 5 Days	+ 5 Days	ET Visit ^c
Type of Visit	In Person ^f	In Person ^f	In Person ^f	In Person ^f	In Person ^f or Virtual ^g	In Person ^f or Virtual ^g	In Person ^f	In Person ^f or Virtual ^g	Virtual ^g	In Person ^f
Written informed consent	X									
Medical history ^h and demography	X									
Documented RSV infection ⁱ	X									
Vital signs ^j	X	X		X			X			X
Height and weight	X	X (weight only)								
Complete physical examination ^k	X	X								X
Symptom-directed physical examination ^l			X	X	X	X	X	X		
Serum ALT, bilirubin, creatinine, and CL _{cr} /eGFR ^m	X									
Chemistry and hematology panels		X		X			X	X ⁿ		X
Urine or serum pregnancy test ^o	X	X					X			X

Study Day		Baseline Day 1 ^{a, c, d}							Day 60 Follow-up Visit	
			Day 3 ^d	Day 5 ^{c, d}	Day 7	Day 10	Day 15 ^c	Day 29		
Visit Window	Screening ^{a, b}		± 1 Day ^e			± 2 Days		+ 5 Days	+ 5 Days	ET Visit ^c
Type of Visit	In Person ^f	In Person ^f	In Person ^f	In Person ^f	In Person ^f or Virtual ^g	In Person ^f or Virtual ^g	In Person ^f	In Person ^f or Virtual ^g	Virtual ^g	In Person ^f
Midturbinate nasal swab ^P		X	X	X	X	X	X			X
Provide nasal self-swab collection kits ^P		X	X (as needed)	X (as needed)	X (as needed)					
Perform nasal self-swab collection training ^P		X	X (as needed)	X (as needed)	X (as needed)	X (as needed)				
Anti-RSV antibody assessment		X								
Sparse PK ^a		X	X	X						X
Intensive PK substudy–venous and capillary blood (optional) ^f		X		X						X
Cytokine profiling		X								
MAVs and hospitalization information ^a		X	X	X	X	X	X	X	X	X
Pre-Existing Symptom Questionnaire		X (predose)								
RiiQ ^g		X	X	X	X	X	X	X		X
PGIS		X	X				X	X		
PGIC ^a				X						X
HCPGIS		X	X	X			X	X		X

Study Day		Baseline Day 1 ^{a, c, d}							Day 60 Follow-up Visit	
			Day 3 ^d	Day 5 ^{c, d}	Day 7	Day 10	Day 15 ^c	Day 29		
Visit Window	Screening ^{a, b}		± 1 Day ^e			± 2 Days		+ 5 Days	+ 5 Days	ET Visit ^c
Type of Visit	In Person ^f	In Person ^f	In Person ^f	In Person ^f	In Person ^f or Virtual ^g	In Person ^f or Virtual ^g	In Person ^f	In Person ^f or Virtual ^g	Virtual ^g	In Person ^f
EQ-5D-5L		X		X			X	X		X
Study drug dispensation		X								
Study drug dosing (ODV or placebo) ^v		X	X	X						
Study drug bottle return ^w				X	X	X	X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X		X
Vital status (alive/dead) and exacerbation history ^x									X	

ALT = alanine aminotransferase; BID = twice daily; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol (5-dimensions, 5-levels); ET = early termination; HCPGIS = Health Care Professional Global Impression of Severity; MAV = medically attended visit; NIPPV = noninvasive positive pressure ventilation; ODV = obeldesivir; PCR = polymerase chain reaction; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); RiiQ = Respiratory Infection Intensity and Impact Questionnaire; RSV = respiratory syncytial virus; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction

- a Screening window is within 24 hours of the Day 1 visit. Day 1 visit may occur on the same day as screening. If the Day 1 and screening visits are the same day, do not repeat assessments.
- b Patients anticipated to be eligible for the study and without documented RSV infection will be consented for RSV testing. Patients who are RSV positive will be approached to consent for the screening and treatment phase of the study.
- c Laboratory tests for safety will be performed on Days 1, 5, and 15, and at the ET visit.
- d All Day 1 assessments excluding PK assessments must occur before administration of the first dose of study drug. Day 3 and 5 assessments should occur prior to the withheld morning or afternoon dose (see footnote u).
- e Day 3, Day 5, and Day 7 visits should be conducted on separate calendar days.
- f In person is defined as a visit at a medical facility or elsewhere by a health care provider (where permitted).
- g Virtual visit is defined as an interaction with a health care professional using telephone or online-based interaction (eg, telehealth, webcast, video conferencing).
- h Medical history will include the date of first RSV symptoms, overall RSV symptoms, all RSV vaccinations prior to screening, baseline characteristics, allergies, and medications taken within 30 days of the screening visit.
- i RSV infection documented by PCR or alternative nucleic acid-based detection.

- j Vital signs include heart rate, body temperature, and blood pressure. Vital signs are collected at in-person visits only.
- k A complete physical examination must include source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, and nails; musculoskeletal; and neurological. Genitourinary and reproductive examination should only be conducted if clinically indicated.
- l Symptom-directed physical examinations will be performed on Days 3, 5, 7, 10, 15, and 29 and only during in-person visits.
- m Serum ALT, bilirubin, serum creatinine, and CLcr/eGFR assessments at screening are not required unless deemed necessary by the investigator to confirm eligibility.
- n Chemistry and hematology laboratory testing on Day 29 is only required if any Day 15 laboratory values were Grades 3 or 4 laboratory abnormalities.
- o At screening, a urine pregnancy test will be performed at the local laboratory for participants assigned female at birth and of childbearing potential. On Days 1 and 15, and ET/unscheduled visits, these participants will have a serum pregnancy test via central laboratory. At screening, a follicle-stimulating hormone test is required to confirm the postmenopausal state in participants younger than 54 years, who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure, as described in the protocol Appendix 11.3.
- p A midturbinate nasal swab will be collected at in-person visits. If the visits on Days 7 or 10 occur virtually, participants will perform a self-swab. Details regarding self-swab collection and analysis are provided in the protocol Section 6.3.9.1.
- q Sparse PK samples will be collected relative to the in-clinic dose on Day 1 at 0.25, 0.75, and 1.5 hours postdose, on Day 3 at predose (< 5 minutes before dose), and on Day 5 at predose (< 5 minutes before dose), 0.75, and 2 hours postdose; $\pm 20\%$ time window will be applied for postdose collection time points. A single PK sample will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose or at the ET visit for all participants who discontinue the study earlier than Day 10.
- r Participants who consent to the optional intensive PK samples and have them collected will not provide samples for sparse PK. In the optional intensive PK substudy: approximately 30 participants at participating study sites will have intensive venous and capillary blood PK samples collected simultaneously relative to the in-clinic dose on Day 1 at 0.25, 0.5, 0.75, 1.5, 3, 4 hours, and on Day 5 at predose (< 5 minutes before dose), 0.25, 0.5, 0.75, 1.5, 3, 4 hours after morning or evening dose at the clinic; $\pm 20\%$ time window will be applied for all postdose collection time points. Single venous and capillary PK samples will be collected on Day 5 (+1 day) for all participants who discontinue the study drug earlier than the last scheduled dose or at the ET visit, for all participants who discontinue the study earlier than Day 10.
- s For the purposes of efficacy analysis, medically attended visit information includes any interactions with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care professional. The nature and cause of the visit should be identified. Medically attended visit and hospitalization information should be collected at all visits except Screening.
- t The RiIQ must be completed prior to dosing on Day 1 and preferably prior to dosing on Days 2-5, at approximately the same time each day, through Day 29. If a participant discontinues from the study early, the participant should complete this questionnaire during the ET visit.
- u The PGIC will be collected only once on Day 5 (or Day 6) visit after the final dose, or on ET visit if the last dose occurs prior to Day 5 visit.
- v Study drug will be administered, without regard to food, orally at doses of 700 mg twice daily on Day 1 (ie, 2 tablets each for 2 administrations) followed by 350 mg twice daily on Days 2 to 5 (ie, 1 tablet each for 8 administrations) for a total of 5 days of drug dosing. On Day 1, 3, and 5, participants will be coming into the clinic in the morning or afternoon and should withhold either their morning or afternoon dose until they arrive in clinic. All assessments on Days 3 and 5 excluding PK assessments should occur prior to the withheld morning or afternoon dose.
- w Study drug bottle should be returned by the participant on Day 5, if the participant has already completed both doses of study drug on that day. If the participant has study drug at the end of the Day 5 visit, the participant may return the study drug bottle on Days 7, 10, or 15. If the Days 7 or 10 visit are virtual, drug accountability should be performed virtually, and the participant will be instructed on returning the study drug bottle on Days 15 or 29.
- x Document history of any chronic disease exacerbations that occurred after Day 29.

Appendix 2. Programming Specifications

- 1) Targeted RSV symptoms are those listed below and will be evaluated in deriving of the primary efficacy endpoint (time to alleviation of all targeted RSV symptoms as measured by RiiQ through Day 15).
 - Nasal congestion
 - Sore throat
 - Cough
 - Wheezing
 - Shortness of breath (dyspnea)
 - Expectoration (sputum production)
- 1) Pre-existing symptom questionnaire (PSQ) assesses symptoms present approximately 1 week prior to development of RSV infection symptoms.
- 2) Alleviation of targeted RSV symptoms
 - a) In participants without *any* targeted pre-existing respiratory symptoms (all targeted symptoms score = 0 in PSQ) or with missing targeted pre-existing respiratory symptoms (all NA in PSQ):
 - i) Targeted symptoms that were not developed (all score = 0 or missing) or scored mild at baseline should be scored as “None” (score = 0) for 2 consecutive assessments in RiiQ.
 - ii) All targeted symptoms scored moderate or severe at baseline should be scored as “None” (score = 0) or “Mild” (score = 1) for 2 consecutive assessments in RiiQ.
 - b) In participants with *at least one* targeted preexisting respiratory symptom:
 - i) Preexisting targeted symptoms that were worse (i.e., scored higher in RiiQ) at baseline should have improved by at least 1 point on the RiiQ Symptom Scale from baseline for 2 consecutive assessments; and
 - ii) Preexisting targeted symptoms that were present but not worse (i.e., having lower or equal score) at baseline should have not worsened from baseline severity for 2 consecutive assessments; and

- iii) Targeted symptoms that were not preexisting (e.g., score = 0 or missing in PSQ) should be scored as “None” (score = 0) or “Mild” (score = 1) on the RiiQ Symptom Scale for 2 consecutive assessments.
1. Targeted symptoms that were not developed (score = 0 or missing) or scored mild at baseline should be scored as “None” (score = 0) for 2 consecutive assessments in RiiQ.
 2. All targeted symptoms scored moderate or severe at baseline should be scored as “None” (score = 0) or “Mild” (score = 1) for 2 consecutive assessments.
- 3) A potential symptom alleviation is defined in Section 6.1.1. For participants without baseline symptoms, all targeted symptoms need to be scored as “None” (score = 0) to be considered as potential symptom alleviation. No missing assessment is allowed between the first date and the last date of potential symptom alleviation included in the calculation.
- 4) The AM/PM assessment window for the RiiQ on each study day is defined in Section 6.1.1.
- Two consecutive assessments are defined as follows and shown in Section 6.1.1:
- Collected on consecutive calendar days and
 - Both assessments in AM windows, or both assessments in PM windows, or first day’s assessment in AM window and second day’s assessment in PM window
- Note: first day’s assessment in PM windows and second day’s assessment in AM window doesn’t qualify as two consecutive assessments.
- 5) Time to alleviation of targeted RSV symptoms (unit = day, keep 8 decimal places in the dataset and display 1 decimal place in TFL outputs)
- a) For participants with alleviation of targeted RSV symptoms by Day 15, use the first event of participant level alleviation status equals “Yes”
- Date and time of symptom alleviation – Date and time of the first dose
- b) For participants who completed Day 15 of the study but without symptom alleviation, time to alleviation of targeted RSV symptoms will be censored at Day 15.
- Date and time of RiiQ assessment at Day 15 – Date and time of the first dose
- Note that, if the RiiQ assessment is missing on Day 15, such participant will be censored at the last RiiQ assessment by Day 15.
- c) For participants who discontinued from the study before Day 15 without symptom alleviation, time to alleviation of targeted RSV symptoms will be censored at the last RiiQ assessment by Day 15.
- Date and time of the last RiiQ assessment – Date and time of the first dose

- d) For participants who experienced intercurrent events, such as hospitalization for the treatment of RSV, all-cause death, or use of rescue medication, or discontinuation for randomized treatment prior to symptom alleviation, the time to alleviation of targeted RSV symptoms will be censored at Day 15.
- 6) Sustained alleviation of targeted RSV symptoms is defined similarly to alleviation of targeted RSV symptoms but for 3 consecutive assessments.
- 7) Time to sustained alleviation of targeted RSV symptoms through Day 15 is calculated in a similar manner to the primary endpoint above.

Three consecutive assessments are defined as follows:

- Collected on consecutive calendar days and
- All qualifying three consecutive assessments are listed below:

AM-AM-AM, AM-PM-PM, PM-PM-PM, AM-AM-PM, AM-PM-AM,
PM-AM-PM,

or

PM-AM-AM-AM, PM-AM-AM-PM, PM-PM-AM-AM, PM-PM-AM-PM, as
PM-AM-AM or PM-PM-AM is not considered as three consecutive assessments
so one additional assessment (either AM or PM) is required.

- 8) RSV-related lower respiratory tract infection (LRTI) is at least two of the following lower respiratory tract (LRT) symptoms at postbaseline, 1 of which must be reported as at least moderate in severity and participant has not met alleviation endpoints (i.e., alleviation of targeted RSV symptoms, sustained alleviation of targeted RSV symptoms).
- new or increased cough
 - new or increased wheezing
 - new or increased shortness of breath
 - new or increased expectoration (sputum production)

Note that: at least two new/increased symptoms (1 of which must be reported as score ≥ 2) at postbaseline (on the same day) compared to PSQ or RiiQ at baseline (whichever is higher in severity score) are required to meet LRTI definition. If a participant achieves alleviation of targeted RSV symptoms after meeting the protocol-defined LRTI definition, then RSV-related LRTI definition is still met.

9) Examples of RSV related LRTI endpoint:

Example	LRT Symptom	PSQ	RiiQ Symptom Score					New or Increased Symptom	LRTI	Reason
			Day 1	Day 2	Day 3	Day 4	Day 5			
1	1	2	2	2	2	2	2	N		
	2	0	0	1	1	1	1	Y		
	3	0	0	1	2	3	2	Y		
	4	0	1	1	1	1	1	N	Y; on Day 3	2 new/increased LRTs and at least 1 moderate at post-baseline
2	1	1	1	1	1	1	1	N		
	2	0	0	3	1	1	1	Y		
	3	0	1	1	2	3	2	Y		
	4	1	1	1	1	3	1	Y	Y; on Day 3	
3	1	0	1	1	1	2	2	Y		
	2	0	0	1	1	1	1	Y		
	3	0	1	1	1	2	2	Y		
	4	1	1	1	1	3	1	Y	Y, on Day 4	
4	1	1	1	1	1	1	1	N		
	2	2	1	2	2	2	2	N		Moderate, but NOT an increased LRT compared to PSQ
	3	0	2	2	2	2	2	N		Moderate, but NOT an increased LRT compared to RiiQ at baseline
	4	0	0	0	1	1	1	Y	N	One more new/increased LRT at score ≥ 2 is required to meet the LRTI definition

PSQ/RiiQ Symptom Score: None = 0, Mild = 1, Moderate=2, and Severe =3.

Yellow highlights indicate those new/increased LRT symptoms on the day that meet LRTI definition.

10) Time to RSV-related LRTI Through Day 29

- a) For participants with RSV-related LRTI by Day 29, use the first date of meeting the LRTI definition

Date and time of meeting the LRTI definition – Date and time of the first dose

- b) For participants who completed Day 29 of the study but without RSV-related LRTI, time to RSV-related LRTI will be censored at Day 29.

Date and time of RiiQ assessment at Day 29 – Date and time of the first dose

Use Day 29 23:59:00 if no Day 29 RiiQ assessment

- c) For participants who discontinued from the study before Day 29 without RSV-related LRTI, time to RSV-related LRTI will be censored at the last RiiQ assessment.

Date and time of the last RiiQ assessment – Date and time of the first dose

Note: for participants who achieved alleviation prior to discontinuing from the study, time to RSV-related LRTI will be censored at the date and time of alleviation achieved.

- d) For participants who experienced intercurrent events (ICEs), such as hospitalization for the treatment of RSV, all-cause death, or use of rescue medication, the time to RSV-related LRTI will be calculated using the date of intercurrent event(s). Use 23:59:00 as the time of intercurrent events.

- e) For participants who meet the LRTI definition on the day or days after achieving the symptom alleviation, time to RSV-related LRTI will be censored at the date and time of alleviation achieved.

11) Any RSV viral load and infectious viral titer samples collected on or after the day when participants are receiving rescue medications (except for Danirixin, Chlorpheniramine maleate and Asapiprant) will be excluded from the viral load or infectious titer analysis.

12) Guidance for consideration of RSV positivity/negativity in an individual sample viral load qRT-PCR result is included below.

- a) Rnase P is a quality check of the sample and should always be positive if the sample was collected correctly. If Rnase P is negative, the result for RSV-A/B should be considered invalid.
- b) RSV viral load values <LLOQ will be reported as “target detected (TD)” or “target not detected (TND)”. The result of “Target Not Detected” without a quantitative result will not be considered as RSV positive.

- c) Under Volume samples resulted as “target detected (TD)” should be considered as RSV-positive qualitative result by RSV RNA Viral Load assay. Under-volume samples are UTM samples with 4 or fewer aliquots.

13) Guidance for consideration of RSV positivity on a participant-level, for determination of the FAPS is included below.

- a) As a primary method, RSV RNA Viral Load in UTM samples will be used to inform RSV status for FAPS determination, per the table below.
- i) If RSV RNA Viral Load in UTM samples result is missing, RSV-positivity will be assumed.
- ii) If RSV RNA Viral Load in UTM samples result is negative, Biofire result will be used as a secondary method to include participants with false-negative UTM Viral Load result.

FAPS (+/-) Determination		UTM Viral Load Result			
		Positive	Negative	Invalid RSV Result due to poor sample quality (RnaseP = TND)	Missing
Biofire Result	Positive	FAPS(+)	FAPS(+)	FAPS(+)	FAPS(+)
	Negative	FAPS(+)	FAPS(-)	FAPS(+)	FAPS(+)
	Assay Failure (NRR)	FAPS(+)	FAPS(-)	FAPS(+)	FAPS(+)
	Missing	FAPS(+)	FAPS(-)	FAPS(+)	FAPS(+)

- b) Participants who are RSV positive include those having viral load detected by qRT-PCR, even if the result is below LLOQ, as well as any participants who have RSV detected by the BIOFIRE multiplex assay.
- c) RSV positivity is determined by either RT-qPCR or BioFire assay in UTM. Participant is defined as RSV positive at baseline when viral load result in UTM is missing. If RSV viral load is negative at baseline in UTM, along with a positive BioFire result, then participant is RSV positive.
- d) In any case of missing RSV RNA viral load result in UTM, the participant is assumed to be RSV positive, regardless of Biofire result.
- e) For viral load assay, either RSV-A or RSV-B positivity is considered as RSV positive for deriving the FAPS. A patient with either RSV-A viral load or RSV-B viral load $\geq$ LLOQ should be included in the VAS. Participants should be excluded from the RSV-A and RSV-B viral load summaries for the opposite RSV subtype.

14) RSV Subtype Classification and Combined RSV Viral Load Calculation:

Below is how to determine the RSV subtype at baseline based on UTM/Dry/Train samples.

RSV Subtype Result: Defined Per Participant		UTM Swab RSV Subtype					
		RSV-A	RSV-B	RSV-A/B Coinfection	RSV-A/B Negative	Invalid RSV Result	Data Pending or Missing
TRAIN/ DRY Swab RSV Subtype	RSV-A	RSV-A Only	RSV-A/B Coinfection	RSV-A/B Coinfection	RSV-A Only	RSV-A Only	RSV-A Only
	RSV-B	RSV-A/B Coinfection	RSV-B Only	RSV-A/B Coinfection	RSV-B Only	RSV-B Only	RSV-B Only
	RSV-A/B Coinfection	RSV-A/B Coinfection	RSV-A/B Coinfection	RSV-A/B Coinfection	RSV-A/B Coinfection	RSV-A/B Coinfection	RSV-A/B Coinfection
	RSV-A/B Negative	RSV-A Only	RSV-B Only	RSV-A/B Coinfection	Not Determined	Not Determined	Not Determined
	Invalid RSV Result	RSV-A Only	RSV-B Only	RSV-A/B Coinfection	Not Determined	Not Determined	Not Determined
	Data Pending or Missing	RSV-A Only	RSV-B Only	RSV-A/B Coinfection	Not Determined	Not Determined	Not Determined

The calculation of combined RSV results in valid samples (when RNase P is positive from the same accession number as RSV-A and RSV-B) is summarized in the table below.

Baseline RSV Subtype Classification	Combined RSV Formula applied to all baseline and post-baseline samples
RSV-A/B Coinfection	Combined RSV = RSV-A imputed + RSV-B imputed
RSV-A only	Combined RSV = RSV-A imputed only
RSV-B only	Combined RSV = RSV-B imputed only
Not Determined	Combined RSV = Blank

RNase P is a quality check of the sample and should always be positive if the sample was collected correctly. If it is negative, we cannot trust the results of the sample and RSV-A/B should be considered invalid. The first step is to determine if RNase P is positive and negative. If positive, then RSV subtype is based on RSV-A and RSV-B character/numeric values reported (compared to LLOQ if needed).

15) The RSV Viral Load (copies/mL) of Combined RSV results will be displayed in the listing per rule below.

RSV-A \ RSV-B	Numeric Result in RSV-B	RSV-B Text = “TD”	RSV-B Text = “TND”
Numeric Result in RSV-A	Combined Numeric Result	Numeric Result in RSV-A + Imputed Numeric Result in RSV-B	Numeric Result in RSV-A
RSV-A Text = “TD”	Numeric Result in RSV-B + Imputed Numeric Result in RSV-A	“TD”	“TD”
RSV-A Text = “TND”	Numeric Result in RSV-B	“TD”	“TND”

16) A general rule to handle samples (including viral load, infectious viral titer, and Biofire multiplex) under the following conditions.

Condition	Exclude from Qualitative analysis (Positive/Negative)	Exclude from Quantitative analysis
frozen time [^] >12 days (dry swab only)	Yes	Yes
RNase P negative	Yes	Yes
Samples collected after rescue medication* received	Yes	Yes
incorrect swab tip type [#]	No	Yes
wrong buffer [§]	No (but Yes if IVT)	Yes
aliquot < 5 (UTM only)	No	Yes
quantitative results unreliable	No	Yes
Participants with low combined RSV VL < 4 log10 copied/mL in UTM at baseline	Yes (if IVT)	Yes (if IVT)
Lab Specimen – Comment = “viral load not reliable” (dry swab only)	Yes	Yes

[^]frozen time = swab frozen date/time – swab collection date/time

*participants receiving additional RSV antiviral treatment should be excluded from both qualitative and quantitative analysis.

[#]exact condition is captured under “Lab – Specimen Comments” in virology datasets

[§]Infectious Viral Titer (IVT) samples should be excluded from both analyses, while viral load samples should be excluded from quantitative analysis only.

17) The following selected subgroups will be listed in the forest plot of primary and two key efficacy endpoints: Age, Sex, Race, Ethnicity, Baseline Combined RSV in UTM, RSV Subtype at Baseline.

18) Targeted RSV symptoms and eGFR by CKD-EPI 2021 at baseline will be treated as ordinal data in the summary of baseline characteristics.

19) Baseline Respiratory Coinfection

Assay	Analyte	Category
BIOFIRE RP2.1 PANEL	ADENOVIRUS	Other Viral Infection
BIOFIRE RP2.1 PANEL	CORONAVIRUS 229E	Other Viral Infection
BIOFIRE RP2.1 PANEL	CORONAVIRUS HKU1	Other Viral Infection
BIOFIRE RP2.1 PANEL	CORONAVIRUS NL63	Other Viral Infection
BIOFIRE RP2.1 PANEL	CORONAVIRUS OC43	Other Viral Infection
BIOFIRE RP2.1 PANEL	MERS-CoV	Other Viral Infection
BIOFIRE RP2.1 PANEL	SARS-CoV-2	SARS-CoV-2
BIOFIRE RP2.1 PANEL	HUMAN METAPNEUMOVIRUS	Other Viral Infection
BIOFIRE RP2.1 PANEL	ENTERO/RHINOVIRUS	Rhinovirus or Enterovirus
BIOFIRE RP2.1 PANEL	INFLUENZA A VIRUS	Influenza A
BIOFIRE RP2.1 PANEL	INFLUENZA A VIRUS SUBTYPE H1	Influenza A
BIOFIRE RP2.1 PANEL	INFLUENZA A VIRUS SUBTYPE H1 (2009)	Influenza A
BIOFIRE RP2.1 PANEL	INFLUENZA A VIRUS SUBTYPE H3	Influenza A
BIOFIRE RP2.1 PANEL	INFLUENZA B VIRUS	Influenza B
BIOFIRE RP2.1 PANEL	HUMAN PARAINFLUENZA VIRUS 1	Other Viral Infection
BIOFIRE RP2.1 PANEL	HUMAN PARAINFLUENZA VIRUS 2	Other Viral Infection
BIOFIRE RP2.1 PANEL	HUMAN PARAINFLUENZA VIRUS 3	Other Viral Infection
BIOFIRE RP2.1 PANEL	HUMAN PARAINFLUENZA VIRUS 4	Other Viral Infection
BIOFIRE RP2.1 PANEL	HUMAN RESPIRATORY SYNCYTIAL VIRUS	RSV*
BIOFIRE RP2.1 PANEL	BORDETELLA PARAPERTUSSIS	Bacterial Infection
BIOFIRE RP2.1 PANEL	BORDETELLA PERTUSSIS	Bacterial Infection
BIOFIRE RP2.1 PANEL	CHLAMYDIA PNEUMONIAE	Bacterial Infection
BIOFIRE RP2.1 PANEL	MYCOPLASMA PNEUMONIAE	Bacterial Infection

* This result should not be used to classify participant into the baseline coinfection category.

20) RSV Rescue Medications

Details of RSV rescue medications are provided in the table below.

Drug Class	Dictionary Level	Preferred Term Codes	Prohibited Ingredient, PREF
Sisunatovir	PREF	15229401001	SISUNATOVIR
Zelicapavir (EDP-938)	PREF	N/A	N/A
Ribavirin	PREF	00816701001	RIBAVIRIN
Favipiravir	PREF	06325301001	FAVIPIRAVIR
Presatovir	PREF	08955601001	PRESATOVIR
Lumicitabine	PREF	09305701001	LUMICITABINE
Rilematovir	PREF	15227101001	RILEMATOVIR
Enzaplatovir	PREF	09305001001	ENZAPLATOVIR
Ziresovir	PREF	15917301001	ZIRESOVIR
Sinogen	PREF	06449501001	INTERFERON ALFA-1B
Interferon Alpha	PREF	05982601001	INTERFERON ALFA
RSV immunoglobulin	PREF	N/A	N/A
Palivizumab	PREF	01462801001	PALIVIZUMAB
Nirsevimab	PREF	15923101001	NIRSEVIMAB
Clesrovimab	PREF	N/A	N/A
Gontivimab	PREF	N/A	N/A
Suptavumab	PREF	09308801001	SUPTAVUMAB
Inarigivir soproxil	PREF	16431601001	INARIGIVIR SOPROXIL
Danirixin	PREF	07842001001	DANIRIXIN
Motavizumab-YTE	PREF	06258001001	MOTAVIZUMAB
Asvasiran	PREF	08683201001	ASVASIRAN
Chlorpheniramine maleate	PREF	00072502001	CHLORPHENAMINE MALEATE
Asapirant	PREF	N/A	N/A
Mindeudesivir hydrobromide	PREF	16035801001	DEUREMIDEVIR HYDROBROMIDE
Astodrimmer	PREF	08634401001	ASTODRIMER
Respiratory syncytial virus immune globulin intravenous (RSV-IGIV)	PREF	07371201001	IMMUNOGLOBULIN ANTI RESPIRATORY SYNCYTIAL VIRUS

N/A: preferred term codes are not available to these drug classes.

Appendix 3. Questionnaires

RiiQ Questionnaires are proprietary and are available on request.