

Janssen Research & Development ***Clinical Protocol**

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rilematovir (JNJ-53718678) in Adult Outpatients with Respiratory Syncytial Virus (RSV) Infection who are at High Risk for RSV-related Disease Progression

PRIMROSE

Effects of Rilematovir in Adult Outpatients with RSV Infection who are at High Risk for RSV-related Disease Progression**Protocol 53718678RSV2008; Phase 2b****JNJ-53718678 (Rilematovir)**

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rilematovir (JNJ-53718678) in Adult Outpatients with Respiratory Syncytial Virus (RSV) Infection who are at High Risk for RSV-related Disease Progression

Effects of Rilematovir in Adult Outpatients with RSV Infection who are at High Risk for RSV-related Disease Progression

Rilematovir (JNJ-53718678) is an investigational, potent small molecule respiratory syncytial virus (RSV) specific fusion inhibitor belonging to the indole chemical class. Rilematovir targets the RSV fusion (F) protein and prevents the conformational changes of the F-protein required for fusion of the viral envelope with the host cell membrane and for cell-to-cell fusion, thereby inhibiting viral replication and syncytia formation.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate efficacy of rilematovir compared to placebo with respect to the time to resolution of RSV lower respiratory tract disease (LRTD) symptoms. 	<ul style="list-style-type: none"> Time to resolution of RSV LRTD symptoms (ie, cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the participant using the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) Symptom Scale. <p>Definition of resolution in participants without pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> <i>All LRTD symptoms in the RiiQ Symptom Scale^a scored as 'None' (score = 0) or 'Mild' (score =1) for at least 24 hours.</i> <p>Definition of resolution in participants with pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> <i>Pre-existing symptoms that were worse at baseline should have improved at least 1 point on the RiiQ Symptom Scale from baseline for at least 24 hours; and</i> <i>Pre-existing symptoms that were not worse at baseline should have not worsened from baseline severity for at least 24 hours; and</i>

^a The RiiQ Symptom scale is a four-item scale (0: no symptoms, 1: mild symptoms, 2: moderate symptoms, 3: severe symptoms).

Objectives	Endpoints
	<ul style="list-style-type: none"> - <i>Symptoms that were not pre-existing at baseline should be scored as 'None' (score = 0) or 'Mild' (score = 1) on the RiiQ Symptom Scale for at least 24 hours.</i>
Secondary	
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir compared to placebo with respect to the incidence of post-baseline RSV-related complications. 	<ul style="list-style-type: none"> • Proportion of participants with post-baseline complications (ie, RSV-related pulmonary and extrapulmonary complications). <ul style="list-style-type: none"> - Pulmonary complications: primary viral pneumonia, bronchitis, respiratory failure, secondary bacterial pneumonia, and exacerbations of underlying chronic pulmonary diseases (such as chronic obstructive pulmonary disease [COPD] and asthma) - Extrapulmonary complications: cardiovascular and cerebrovascular disease events, congestive heart failure (CHF) or exacerbation of underlying CHF, acute exacerbation of chronic kidney disease, severe dehydration, decompensation of previously controlled diabetes mellitus, and other airway infections (eg, sinusitis). -
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir as compared to placebo on medical resource utilization (MRU) with respect to respiratory therapeutic interventions associated with RSV-related disease progression. 	<ul style="list-style-type: none"> • Proportion of participants with new antibiotic use, or new or increased use in bronchodilator/nebulizer, systemic corticosteroids, or home oxygen supplementation.
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir as compared to placebo on MRU with respect to medically attended visits associated with RSV-related disease progression. 	<ul style="list-style-type: none"> • Proportion of participants with unscheduled outpatient clinic visits, emergency room visits or hospitalization for respiratory infection.
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir as compared to placebo on the overall RSV-related disease progression. 	<ul style="list-style-type: none"> • Proportion of participants meeting a composite endpoint of either developing RSV-related complications (pulmonary & extra pulmonary) and/or needing RSV-related medical attendance.
<ul style="list-style-type: none"> • To evaluate the safety and tolerability of rilematovir. 	<ul style="list-style-type: none"> • Safety and tolerability, as assessed by adverse events (AEs), clinical laboratory testing, electrocardiograms (ECGs), physical examination, and vital signs.

Objectives	Endpoints
<ul style="list-style-type: none"> To evaluate the effect of rilematovir compared to placebo on the clinical course of RSV infection. 	<ul style="list-style-type: none"> Change from baseline over time in severity of the RSV LRTD symptoms as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue) as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of the overall RSV symptoms (upper respiratory tract disease [URTD] {sore throat and nasal congestion}, LRTD, and 2 systemic symptoms [feeling feverish and fatigue]) as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of all RSV symptoms as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of each separate RSV LRTD symptom as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of respiratory infection symptoms as assessed by the participant using the Patient Global Impression of RSV Severity (PGI-S) Scale. <p>Definition of resolution in participants without pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> <i>All LRTD symptoms in the RiiQ Symptom Scale^a scored as 'None' (score = 0) or 'Mild' (score = 1) for at least 24 hours.</i> <p>Definition of resolution in participants with pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> <i>Pre-existing symptoms that were worse at baseline should have improved at least 1 point on the RiiQ Symptom Scale from baseline for at least 24 hours; and</i> <i>Pre-existing symptoms that were not worse at baseline should have not worsened from baseline severity for at least 24 hours, and,</i>

^a The RiiQ Symptom scale is a four-item scale (0: no symptoms, 1: mild symptoms, 2: moderate symptoms, 3: severe symptoms).

Objectives	Endpoints
	<ul style="list-style-type: none"> – <i>Symptoms that were not pre-existing at baseline should be scored as ‘None’ (score = 0) or ‘Mild’ (score = 1) on the RiiQ Symptom Scale for at least 24 hours.</i> • Time to return to pre-existing health (status) for all RSV symptoms as assessed by the participant using the RiiQ™ Symptom Scale. • Time to improvement in RSV disease as assessed by the participant using the Patient Global Impression of Change (PGI-C) Scale.
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir compared to placebo on Health-Related Quality of Life (HRQOL). 	<ul style="list-style-type: none"> • Change from baseline over time for the HRQOL as assessed by participants using the EQ-5D-5L and RiiQ™ Impact Scales. • Time to return to usual health as assessed by the participant using the ‘Adult RSV Return to Usual Health’ question. • Time to return to usual activities as assessed by the participant using the ‘Adult RSV Return to Usual Activities’ question. • Time to no or mild impact of RSV-related disease on daily activities, emotions, and social relationships as assessed by the participant using the RiiQ™ Impact Scales.
<ul style="list-style-type: none"> • To evaluate the antiviral effect of rilematovir as measured by RSV viral load in bilateral nasal mid-turbinate swab samples by quantitative revers transcription polymerase chain reaction (qRT-PCR) assay. 	<ul style="list-style-type: none"> • Respiratory syncytial virus viral load area under the curve from immediately prior to first dose of study intervention (baseline) through Day 3, Day 5, Day 8. • Change from baseline over time in RSV viral load. • Proportion of participants with undetectable RSV viral load at each time point that a swab is planned to be collected.
<ul style="list-style-type: none"> • To evaluate the emergence of mutations in the viral genome potentially associated with resistance to rilematovir. 	<ul style="list-style-type: none"> • Post-baseline sequence changes in the RSV F gene.
<ul style="list-style-type: none"> • To evaluate the pharmacokinetics (PK) of rilematovir. 	<ul style="list-style-type: none"> • Pharmacokinetic parameters of rilematovir (ie, predose plasma concentration [C_{trough}], maximum plasma concentration [C_{max}], and area under the curve of administration up to 12 hours post dosing [AUC_{0-12h}]).

Objectives	Endpoints
<ul style="list-style-type: none"> To evaluate the impact of rilematovir compared to placebo on MRU. 	<ul style="list-style-type: none"> Number and type of medical encounters. Shift in any care setting (e.g. from no assistance to use of skilled home nurse or assisted home living). Proportion of participants requiring hospitalization for respiratory or other reasons and duration of hospitalization (total days length of stay, including incidence and where feasible duration by wards, eg, intensive care unit [ICU]). Incidence and duration of treatment-emergent use of antibiotics. Incidence and duration of treatment-emergent new use or increased dose of systemic or inhaled corticosteroids and bronchodilators. Proportion of participants with new or increased use of oxygen therapy. Duration of oxygen supplementation. Duration of selected post-baseline emergent (after start of study intervention) MRU.
Exploratory	
<ul style="list-style-type: none"> To explore the relationship between antiviral activity and the primary and key secondary clinical outcomes. 	<ul style="list-style-type: none"> Respiratory syncytial virus viral load-based endpoints and primary and key secondary clinical course endpoints.
<ul style="list-style-type: none"> To explore the impact of rilematovir compared to placebo on RSV disease-related progression and complications. 	<ul style="list-style-type: none"> The proportion of participants progressing to ICU including the need for mechanical ventilation (yes or no). All-cause mortality up to Day 35.
<ul style="list-style-type: none"> To evaluate the impact of rilematovir compared to placebo on the clinical course of disease using the Clinician Symptom Score (CSS). 	<ul style="list-style-type: none"> Change from baseline over time in the CSS as assessed by a Clinician Questionnaire.
<ul style="list-style-type: none"> To explore the relationship between PK of rilematovir and pharmacodynamics (PD) (selected antiviral activity, clinical outcomes, and safety parameters). 	<ul style="list-style-type: none"> Pharmacokinetic/PD analysis of plasma concentration-time data of rilematovir and selected clinical outcomes, antiviral activity, and safety parameters.
<ul style="list-style-type: none"> To explore the impact of rilematovir compared to placebo on hours missed from work (by all members of the participant's household, including the participant, if employed). 	<ul style="list-style-type: none"> Hours missed from work due to the participant's RSV infection by all members of the participant's household, including the participant, if employed.

Hypothesis

The primary hypothesis of this study is that rilematovir reduces the time to resolution of the RSV LRTD symptoms compared to placebo, as assessed by a patient-reported outcome (PRO) measure (RiiQ™) in adult outpatients with at least moderate RSV disease and who are at high risk for RSV disease-related progression.

OVERALL DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy, safety, and tolerability of rilematovir at a dose of 250 mg twice daily administered for 7 days in outpatient adults (≥ 18 to ≤ 85 years of age) who are at high risk of RSV-related disease progression, and who have at least moderate RSV disease (LRTD) due to RSV infection. Moderate RSV disease is defined as having at least any 2 of the symptoms of LRTD (*cough, wheeze, coughing up phlegm, short of breath*), one of which must be scored as at least ‘moderate’ if the symptoms did not pre-exist before RSV onset, OR one of which must be scored worse than usual if the symptoms pre-existed as determined by the participant's ratings of the RiiQ Symptom Scale and the Pre-Existing Symptom Questionnaire in the ePRO device.

A target of 180 participants who meet all eligibility criteria will be randomized in a 2:1 ratio to receive 1 of the following 2 treatments:

- Treatment A: rilematovir 250 mg twice daily for 7 days (n = 120)
- Treatment B: placebo twice daily for 7 days (n = 60)

Randomization to study intervention treatment should occur within 72 hours after onset of any of the RSV symptoms or worsening of pre-existing symptoms.

High-risk condition(s) for RSV-related disease progression is defined as:

- Presence of any of the underlying high-risk comorbid cardiopulmonary conditions (COPD, asthma, or CHF) AND/OR
- ≥ 65 years of age (elderly participants)

The study population should consist of at least 50% of participants with randomization ≤ 48 hours since onset of RSV symptoms.

All study procedures will be conducted as stipulated in the Schedule of Activities of the body of the document.

An Independent Data Monitoring Committee will be commissioned for this study to monitor safety data on a regular basis.

A separate Substudy to explore the use of Biosensors for monitoring cardio-respiratory parameters will be performed at selected study sites in a subset of participants who provide specific consent

for this assessment. Details, including objectives and study design, will be described in a separate Substudy protocol.

A second Substudy with Qualitative Patient Interviews will be performed at selected study sites in a subset of participants who provide specific consent for this assessment. This Substudy will gain insight in the participants experience throughout the clinical course of their RSV infection, and to guide interpretation of treatment outcomes and study endpoints. Details, including objectives and study design, will be described in a separate Substudy protocol.

NUMBER OF PARTICIPANTS

A target of 180 participants who are at high risk for RSV-related disease progression will be randomly assigned in a 2:1 ratio (active:placebo) in this study with approximately 120 participants planned in the rilematovir group and approximately 60 participants in the placebo group.

High-risk condition(s) for RSV-related disease progression is defined as:

- Presence of any of the underlying high-risk comorbid cardiopulmonary conditions (COPD, asthma, or CHF) AND/OR
- ≥ 65 years of age (elderly participants)

Randomization will be stratified by high-risk (<65 years of age with underlying high-risk comorbid cardiopulmonary conditions [COPD, asthma, or CHF] versus ≥ 65 years of age without underlying comorbid cardiopulmonary conditions versus ≥ 65 years of age with underlying comorbid cardiopulmonary conditions), and time since symptom onset (≤ 48 hours versus >48-72 hours).

INTERVENTION GROUPS AND DURATION

Eligible participants will be randomized in a 2:1 ratio to receive either Treatment A (rilematovir 250 mg twice daily) or B (matching placebo twice daily).

The study will include a screening period (Day -1 to Day 1), a Treatment Period (Day 1 to Day 7/8 [depending on timing of first dose]), and a Follow-up Period (Day 8/9 to Day 35 [± 3]). In general, the total study duration for each participant will be 35 (± 3) days. The study is considered complete with the completion of the last study assessment for the last participant in the study.

Description of Interventions

Arm Name	Treatment A	Treatment B
Intervention Name	Rilematovir (JNJ-53718678)	Placebo
Type	Drug	Drug
Dose Formulation	Oral film-coated tablet	Oral film-coated tablet
Unit Dose Strength(s)	eq. 125-mg	Matching placebo

Arm Name	Treatment A	Treatment B
Dosage Level(s)	250 mg bid for 7 days (dose reduction to 125 mg bid if coadministration with moderate or strong CYP3A4 inhibitors is started or continued during study intervention treatment) ^a	Matching placebo bid for 7 days
Route of Administration	Oral	Oral
Use	Experimental	Placebo
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product	No	No
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	The oral film-coated tablets are packaged in high-density polyethylene (HDPE) bottles with child-resistant screw caps with 2 g of desiccant.	
	Labels will contain information to meet the applicable regulatory requirements.	
Delivery Instructions	Do not crush tablets. All study drugs will be taken orally with a glass of water.	
Food/Fasting Requirement	Regardless of food administration	
Other Requirements	Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM)	
^a Refer to the body of the document for details regarding the coadministration of moderate or strong CYP3A4 inhibitors during the study. Investigators must review the concomitant medications at screening and consult the sponsor as needed.		

EFFICACY EVALUATIONS

Clinical Course and Severity of RSV Infection

The impact of rilematovir treatment on RSV disease severity and duration will be assessed by participants in the ePRO device using the:

- RiiQ™ Symptom Scale
- Pre-Existing Symptom Questionnaire
- 2 Patient Global Impression (PGI) questions about the overall severity and change in RSV disease: PGI of severity (PGI-S) and PGI of change (PGI-C) in RSV disease

The impact of rilematovir treatment on RSV disease severity will be assessed by the clinician by rating the severity of the RSV LRTD sign/symptoms in the study participants using the Clinician Symptom Score (CSS).

Clinical evaluation includes vital sign assessments (ie, body temperature, respiratory rate, pulse/heart rate, peripheral capillary oxygen saturation [SpO₂]) and physical examination assessments (ie, presence of wheezing or crackles/rhonchi) as measured during site visits. Clinical

evaluation also includes RSV-related complications, need for respiratory therapeutic interventions (including antibiotics), and medical attendance for respiratory infections.

Functioning and Health-related Quality of Life (HRQOL)

The impact of treatment on the degree to which RSV symptoms interfere with the participant's routine functioning and HRQOL will be assessed by participants in the ePRO device using the:

- Hours Missed from Work question
- RiiQ™ Impact Scales
- 5 level EuroQol® 5 Dimension (EQ-5D-5L) questionnaire

Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal secretions, obtained via a bilateral nasal mid-turbinate swab sample, will be measured at the central laboratory using a quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay. The qRT-PCR used to determine RSV viral load will also provide information on the RSV subtype. Bilateral nasal mid turbinate swab specimens for the determination of RSV viral load will be collected at several time points during the study as indicated in the Schedule of Activities of the body of the document.

PHARMACOKINETIC EVALUATIONS

Blood samples will be used to evaluate the PK of rilematovir. Pharmacokinetic parameters will be determined using a population PK (popPK) approach by means of nonlinear mixed-effects modeling. The PK/PD relationship of rilematovir exposure (area under the plasma concentration-time curve from time 0 to 24 hours after dosing [AUC_{0-24h}], maximum plasma concentration [C_{max}], or minimum plasma concentration [C_{min}]) with selected efficacy (change in viral load from baseline and clinical outcomes) and safety (including laboratory abnormalities and AEs) parameters will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD analysis will be reported in a separate report.

Venous blood samples of approximately 2 mL per sample will be collected for measurement of plasma concentrations of rilematovir at time points indicated in the Schedule of Activities in the body of the document. Samples can also be used for the analysis of metabolites of rilematovir, excipients, protein binding, or endogenous markers for enzymes or transporters involved in the metabolism and distribution of rilematovir, at the discretion of the sponsor.

BIOMARKERS

Blood samples for biomarker research will be collected at time points indicated in the Schedule of Activities in the body of the document. and may be used for biomarker research (eg, host ribonucleic acid [RNA], proteins including cytokines, cellular phenotyping), on the premise that these markers may play a role in the treatment response, safety, or PK of rilematovir, or in RSV-related disease. Leftover nasal mid-turbinate swabs and blood samples collected for other

testing may be used as well for the same purpose. Analyses of biomarkers will be conducted at the sponsor's discretion and may be reported separately from this study.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization data, associated with medical encounters, will be collected in the electronic case report form (eCRF) by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will be used to conduct secondary efficacy analyses (use of respiratory therapeutic interventions as well as medically attended visits) and may be used to conduct exploratory economic analyses. Medical Resource Utility will include:

- Number and duration of medical care encounters (eg, increased nursing visits at home, emergency room visit).
- Number (proportion) of participants requiring hospitalization for respiratory/other reasons and duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit). In the event of hospitalization during the study, investigators must make every effort to collect details of hospitalization as feasible, including the reason and duration of hospitalization.
- Incidence of antibiotic treatment.
- Any new or increased use of systemic or inhaled corticosteroids and bronchodilators use.
- New or increased use of oxygen therapy.
- Duration of selected post-baseline (after start of study intervention) MRU.

SAFETY EVALUATIONS

Safety and tolerability will be assessed throughout the study from signing the main informed consent form (ICF) until the participant's last study-related activity. For participants having signed a diagnostic ICF, only procedure-related AEs will be reported.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability:

- AEs, serious AEs (SAEs), and deaths.
- Clinical laboratory tests (blood and urine).
- ECG (12-lead).
- Vital signs.
 - Vital signs assessments performed as part of the clinical course of RSV infection related assessments (body temperature, heart/pulse rate, respiratory rate, and SpO₂).

- Additional vital signs assessments: systolic blood pressure and diastolic blood pressure.
- A complete physical examination (including height and body weight measurements) and targeted physical examination.
- Pregnancy.

STATISTICAL METHODS

Sample Size Determination

The study will aim to enroll approximately 180 participants in a 2:1 ratio to rilematovir 250 mg twice daily (approximately 120 participants) and placebo (approximately 60 participants).

The sample size calculation is based on the primary efficacy endpoint, which is the time to resolution of RSV LRTD symptoms from randomization up to Day 35 in the intention-to-treat-infected (ITT-i) analysis set.

With a sample size of 180 participants, there is an 80% probability to demonstrate a reduction of at least 20% in the primary efficacy endpoint when the true effect is 30%. As further guidance for the sample size of this study, the power to detect a treatment difference for the primary efficacy endpoint is also calculated.

An accelerated failure time (AFT) model with underlying log-normal distribution for the time to resolution is assumed with a median in a placebo arm of 14 days and a scale parameter of 0.8 (as observed in Study 51738678RSV2004). Using the Gehan-Wilcoxon test to analyze the data and based on the assumptions that the time to recovery is improved by 30%, that approximately 10% of the total enrolled participants may not be centrally confirmed RSV positive, and that 5% of patients may drop out of the study early before reaching resolution of their RSV LRTD symptoms, a sample size of 180 participants (randomized in a 2:1 ratio to rilematovir 250 mg twice daily and placebo) will have an estimated power of 80% as based on 10,000 simulations using a 10% 2-sided significance level. The power was estimated as the number of simulated studies where the 2-sided p value from the Gehan-Wilcoxon test was <0.1 out of the 10,000 simulated datasets.

Efficacy Parameters

Primary Endpoint

The primary endpoint is the time to resolution of RSV LRTD symptoms from initiation of study treatment up to Day 35 as assessed by the participant using the RiiQ™ Symptom Scale. The RSV LRTD symptoms are defined as the following symptoms from the RiiQ Symptom Scale: cough, short of breath, wheezing, and coughing up phlegm (sputum).

Resolution of RSV LRTD symptoms in participants without pre-existing conditions is reached when all RSV LRTD symptoms in the RiiQ Symptom Scale are scored as ‘None’ (score = 0) or ‘Mild’ (score =1) for at least 24 hours.

Resolution of RSV LRTD symptoms in participants with pre-existing conditions is reached when:

- Pre-existing symptoms that were worse at baseline have improved at least 1 point from baseline for at least 24 hours; and
- Pre-existing symptoms that were not worse at baseline have not worsened from baseline severity for at least 24 hours; and
- Symptoms that were not pre-existing at baseline should be scored as ‘None’ (score = 0) or ‘Mild’ (score =1) for at least 24 hours.

The primary efficacy endpoint will be estimated using an AFT model adjusted by the randomization factors (high-risk and time since symptom onset) and baseline RSV LRTD symptom domain score.

Kaplan-Meier curves as well as Kaplan-Meier estimates of median time to resolution will also be provided.

Secondary Endpoint

The proportion of participants with complications (including all RSV-related pulmonary and extrapulmonary complications) from initiation of study treatment up to Day 35 will be analyzed using a logistic regression. Stratification factors will be added as covariates to the model. Similarly, all the secondary binary endpoints will be analyzed using a logistic regression.

All time-to-event secondary efficacy analyses will be analyzed similarly to the primary endpoint.

Changes from baseline over time as assessed by PRO questionnaires will be analyzed using a mixed-effect model with repeated measurements (MMRM). This analysis includes fixed categorical effects of treatment, randomization strata, time, and treatment-by-time interaction, as well as the continuous covariates of baseline score and baseline score-by-time interaction.

Antiviral Activity

Antiviral activity will be determined based on measurements of RSV viral load in nasal mid-turbinate swab samples by a qRT-PCR assay. These data will be analyzed graphically. For continuous variables, descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented.

Mean log₁₀ viral load values over time will be analyzed using MMRM. Differences between intervention groups in viral load, and the difference in the RSV viral load AUC through Days 3, 5, and 8 between intervention groups will be derived using appropriate contrasts deriving least square mean differences, including the 90% 2-sided confidence intervals.

The relationship between antiviral activity and baseline characteristics, including but not limited to RSV viral subtype and genotype will be explored.

Viral Sequencing

The results of viral sequencing will be evaluated by the sponsor virologist. Pre-treatment genetic variations and relevant post-baseline changes in the RSV F gene (and other regions of the RSV genome, if applicable and on request of the sponsor virologist) will be tabulated and described. The effect of pre-treatment RSV F protein genetic variations and relevant post-baseline RSV F protein amino acid changes on antiviral response and/or clinical outcomes will be explored.

Safety Analysis

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the end of the study is considered to be treatment-emergent. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided (as defined in the Appendix of the document).

The laboratory abnormalities will be determined according to the criteria specified in the Division of Microbiology and Infectious Diseases adult toxicity table (as defined in the Appendix of the document) and in accordance with the normal ranges of the clinical laboratory if no gradings are available.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations and pre- vs post-intervention cross-tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

Vital Signs

Descriptive statistics of respiratory rate, pulse/heart rate, SpO₂, body temperature, and blood pressure (systolic and diastolic) will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized by treatment.

Other Analysis

Pharmacokinetic Analyses

Pharmacokinetic analysis set of plasma concentration-time data of rilematovir will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a PK analysis set plan and the results of the PK analysis set will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of rilematovir population-derived exposure parameters with selected antiviral activity parameters, clinical outcomes, and safety endpoints will be explored. These relationships will be presented in a tabular and/or graphical display. The results of the PK/PD analysis may be conducted at the sponsor's discretion and reported separately from this study.

Biomarkers Analyses

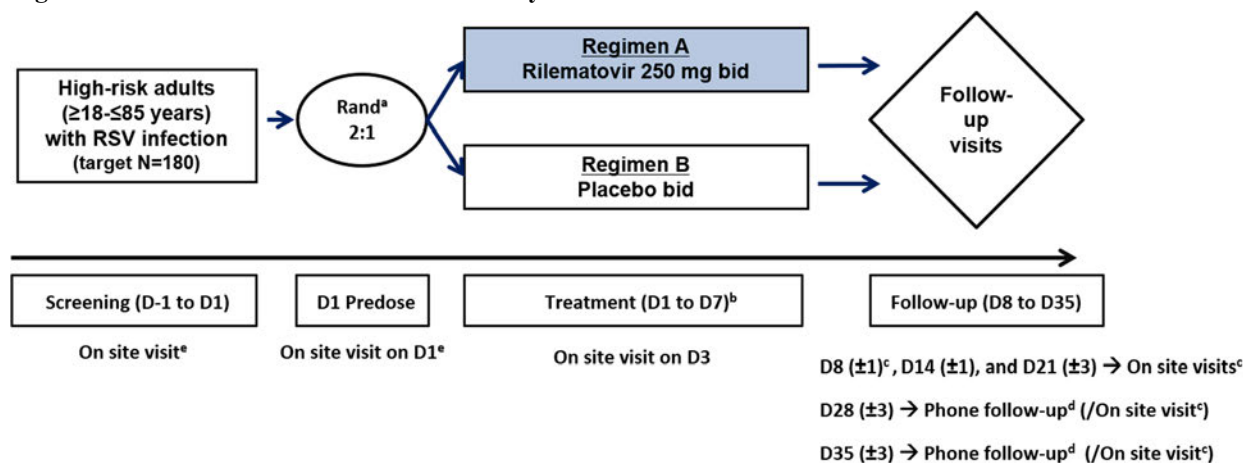
Statistical approaches to explore correlations between clinical outcome, viral load, and biomarkers in blood and nasal mid-turbinate swabs vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences among study participants. Analyses may be conducted at the sponsor's discretion and reported separately from this study.

Interim Analysis

Interim analyses may be conducted at sponsor's discretion when at least approximately 65% of participants are enrolled to allow preparation towards a Phase 3 study design. The interim analysis, performed by the sponsor in an unblinded manner, will preferably be conducted at the end of a northern or southern hemisphere RSV season.

1.2. Schema

Figure 1: Schematic Overview of the Study



CHF: congestive heart failure; COPD: Chronic Obstructive Pulmonary Disease; D: day; bid: twice daily; N: number of participants; rand: randomization; RSV: respiratory syncytial virus.

- ^a Patients should be randomized within 72 hours of RSV sign/symptom onset. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the standard-of-care sample or pre-screening sample used for local RSV diagnosis, whichever comes first. The randomization will be stratified by the following factors: high-risk (<65 years of age with underlying high-risk cardiopulmonary conditions [COPD, asthma, or CHF] versus ≥65 years of age without underlying high-risk conditions versus ≥65 years of age with underlying high-risk conditions) and time since symptom onset (≤48 hours versus >48-72 hours).
- ^b First study intervention administration should start as soon as possible, but no later than 4 hours after randomization. Participants will receive either rilematovir or matching placebo for 7 days twice daily. For participants who receive only 1 dose of study intervention on Day 1 (PM), dosing should continue until the morning of Day 8 (AM) so that all participants receive 14 consecutive doses in total.
- ^c If feasible and allowed by local regulations, home visits by the nursing/ study site personnel are allowed instead of on-site visits.
- ^d If feasible, and allowed per country-specific regulations, digital (eg. videocall) follow-up may be done instead of phone follow-up.
- ^e The screening and D1 predose visit should preferably be done on the same calendar day.

1.3. Schedule of Activities

Phase	Screening	Predose ^a	Treatment Phase ^b				Follow-up ^b						
Day	-1 to 1 ^{a,c}	1	2	3	4-7 ^d	8 (+1) ^d	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3)	35 (±3)
	Screening On-site ^e	Predose On-site ^{a,e}	Treatment On-site	On-site visit ^f		On-site visit ^f		On-site visit ^f		On-site visit ^f		Phone follow-up (/On-site visit) ^{f,g}	Phone follow-up (/On-site visit) ^{f,g}
Study Procedures													
Screening/Administrative													
Diagnostic ICF (optional) ^c	X												
Informed Consent (ICF)	X												
Eligibility criteria ^g	X												
Local RSV diagnosis in bilateral nasal MT swab or SOC sample ^p	X												
Bilateral nasal MT swab for local RSV diagnosis and central testing (viral load and viral sequencing) ^{p,q}	X												
Set-up and training on ePRO device ⁱ	X												
RiiQ™ Symptom Scale ⁱ	X												
Pre-Existing Symptom Questionnaire ^{i,j,k}	X												
Participant characteristics and demographics	X												
Medical history/smoking habits/prior medications	X												
Blood sampling for HIV-1 and -2, hepatitis A, B & C serology	X												

Phase	Screening	Predose ^a	Treatment Phase ^b				Follow-up ^b						
Day	-1 to 1 ^{a,c}	1	2	3	4-7 ^d	8 (+1) ^d	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3)	35 (±3)
	Screening On-site ^e	Predose On-site ^{a,e}	Treatment On-site		On-site visit ^f		On-site visit ^f		On-site visit ^f		On-site visit ^f	Phone follow-up (/On-site visit) ^{f,g}	Phone follow-up (/On-site visit) ^{f,g}
Physical examination ^{hh}	X												
Urine pregnancy test ⁿ	X									X			
FSH test ^o	X												
Randomization		X ^r											
Study Intervention Administration													
Dosing study intervention ^t			X/bid ^t	bid	bid	bid	(X) ^t						
Provision of study intervention for daily use at home ^u			X										
Monitor compliance of study intervention intake			Throughout treatment phase										
Return of remainder of study intervention and compliance check							X						
Efficacy Assessments													
Clinical evaluation ^v	X	X ^w			X		X		X		X	(X) ^z	(X) ^z
Clinician Symptom Score ¹	X	X ^w			X		X		X		X	X ^m	X ^m
Bilateral nasal MT swab for RSV diagnosis confirmation, RSV viral load, presence of other respiratory viruses or bacteria, viral sequencing (centrally) ^{q,bb}		X ^{aa}											
Bilateral nasal MT swab for RSV viral load and viral sequencing (centrally) ^{q,cc,bb}				Home swab on Day 2	X	Home swab on Day 5	X		X		X		

Phase	Screening	Predose ^a	Treatment Phase ^b				Follow-up ^b							
Day	-1 to 1 ^{a,c}	1		2	3	4-7 ^d	8 (+1) ^d	9-13	14 (±1)	15- 20	21 (±3)	22- 27	28 (±3)	35 (±3)
	Screening On-site ^e	Predose On-site ^{a,e}	Treatment On-site		On- site visit ^f		On-site visit ^f		On- site visit ^f		On-site visit ^f		Phone follow- up (/On-site visit) ^{f,g}	Phone follow- up (/On-site visit) ^{f,g}
RiiQ™ Symptom Scale ⁱ		X ^{w,x}		2x daily (bid) on Day 2 through Day 14					1x daily (qd) on Day 15 to Day 35 visit ^t					
RiiQ™ Impact Scales ⁱ		X		qd on Day 2 through Day 35										
PGI-S ⁱ		X	X	qd on Day 2 through Day 35										
PGI-C ⁱ				qd on Day 2 through Day 35										
EQ-5D-5L ⁱ		X			X		X		X		X			X
Employment status ⁱ		X												
Hours missed from work ⁱ		(X ^y)		(qd on Day 2 through Day 35 ^y)										
Return to usual activities ⁱ				qd on Day 2 through Day 35										
Return to usual health ⁱ				qd on Day 2 through Day 35										
Check ePRO completion compliance ^{ee}	Throughout the study via ePRO vendor portal													
Return ePRO device ^{dd,ff}														X
MRU	Throughout the study													
Safety Assessments														
Systolic and diastolic blood pressure ^{gg}	X				X		X		X		X		(X ^z)	(X ^z)
Physical examination ^{hh}	X				X		X		X		X		(X ^z)	(X ^z)
ECG (12-lead) ⁱⁱ	X		X ^{jj}		X		X		X					
Clinical Laboratory Assessments														
Blood sampling for hematology and biochemistry ^{kk,ll}	X ^{mm}						X				X		(X ^z)	(X ^z)
Urinalysis ^{ll,nn}	X						X				X			

Phase	Screening	Predose ^a	Treatment Phase ^b				Follow-up ^b							
Day	-1 to 1 ^{a,c}	1	2	3	4-7 ^e	8 (+1) ^d	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3)	35 (±3)	
	Screening On-site ^e	Predose On-site ^{a,e}	Treatment On-site		On-site visit ^f		On-site visit ^f		On-site visit ^f		On-site visit ^f		Phone follow-up (/On-site visit) ^{f,g}	Phone follow-up (/On-site visit) ^{f,g}
Pharmacokinetics														
Sparse blood sampling for PK of rilematovir ^{oo}			X		X		X							
Biomarker research														
Blood sampling for biomarker research ^{pp}	X				X		X				X			
Continuous Participant Review														
Adverse events ^{qq}	Throughout the study													
Concomitant medication ^{rr}	Throughout the study													

AE: adverse event, bid: twice daily, CSS: Clinician Symptom Score, eCRF: electronic case report form, ECG: electrocardiogram, EQ-5D-5L: 5-Level EuroQol® 5-Dimension, FSH: follicle stimulating hormone, HIV: human immunodeficiency virus, ICF: Informed Consent Form, MRU: medical resource utilization, MT: mid-turbinate, PGI-C: Patient Global Impression of Change, PGI-S: Patient Global Impression of Severity, PK: pharmacokinetics, ePRO: (electronic) patient-reported outcome, qd: once daily, QTcF: QT interval with Fridericia's correction, RiiQ: Respiratory Infection Intensity and Impact Questionnaire, RNA: ribonucleic acid, RSV: respiratory syncytial virus, SOC: standard-of-care.

Note: If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ePRO, ECG, vital signs, bilateral mid-turbinate nasal swab, blood sampling, physical examination, and CSS.

Footnotes:

- Screening/predose assessments can begin after main ICF signature and must finish prior to first study intervention administration. These assessments and eligibility confirmation are permitted to continue into the next calendar day, but then randomization and first study intervention administration will promptly follow, and this day is considered Day 1.
- If a participant prematurely discontinues study intervention for any reason (except withdrawal of consent), he or she will be asked to continue with their remaining study visits and assessment schedule. Participants who withdraw consent during the treatment or follow-up phase will be offered an optional Safety Follow-up visit which will consist of the same assessments as at the Final Study Visit (Day 35).
- Participants may initially sign a diagnostic ICF to allow collection and testing of study-specific nasal MT swabs for the purpose of study eligibility. This does not apply if a diagnostic sample was taken as standard-of-care (SOC) within 24 hours of screening start and yields a positive RSV result.
- Window applies to all clinical assessments of the on-site visit (or home visit, if applicable, see footnote ^e), except the daily completion of the PRO questionnaires.
- The screening and predose visit should preferably be done on the same calendar day.
- On-site visits are recommended on the specified visit days. If feasible and allowed by local regulations, home visits by the nursing/study site personnel are allowed instead of on-site visits.

- g. All participants will complete assessments from Day 1 through Day 35 as per the Schedule of Activities. On Day 28 and Day 35, all participants will be contacted by the study site personnel for a telephone (or other digital call, if possible) follow-up visit to assess the clinical status, MRU and to check for any AEs including RSV-related complications. The phone follow-up visit may be replaced by an on-site visit (or home visit by the nursing/study site personnel, if feasible), at the discretion of the investigator, for safety follow-up in case participants had ongoing AEs or other ongoing laboratory, vital signs or ECG-related abnormalities at the previous visit or for practical reasons (such as return of ePRO device).
 - h. Procedures performed as part of SOC within approximately 48 hours prior to screening completion (ie, randomization) may be used in determining study eligibility. Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.
 - i. Participants will be completing ePRO assessments on an electronic device. Sites will ensure participants are trained in the use of the device before completing ePRO assessments (ie, Employment status, RiiQ™ Symptom and Impact Scales, PGI-S, PGI-C, Hours missed from work, return to usual activities, return to usual health, and EQ-5D-5L) on the device. The ePRO assessments will be completed by each participant in a language in which the participant is fluent; if no appropriate language version is available for the ePRO assessments, the participant should not be enrolled in this study. If a participant requires assistance entering responses in the electronic device, his/her spouse, partner, relative, or other caregiver or member of the study team who is trained on the use of the device and in the interview procedure can interview the participant and enter the participant's responses on the electronic device on the participant's behalf.
- Note:** If participant is clinically stable and there is no safety concern, it is recommended that daily ePRO entries for RiiQ symptom scale as well as scheduled on-site visits are performed before use of any concomitant medication(s) for symptom relief (e.g. bronchodilators, cough medication).
- j. The Pre-Existing Symptom Questionnaire will be completed at screening after the participant completes the RiiQ™ Symptom Scale.
 - k. Assessment of inclusion criterion n°3 (RSV symptoms severity) must be performed before randomization through the evaluation of the participant's answers to RiiQ™ Symptom Scale and Pre-Existing Symptom Questionnaire.
 - l. Investigator will evaluate severity of clinical signs/symptoms of RSV using the Clinician Symptom Score (CSS) questionnaire based on clinical evaluation of the participant at the specified on-site visits as per the Schedule of Activities. If an on-site visit is not feasible for the participant, option for home visit & evaluation by nursing staff under remote supervision of the physician will be allowed. At Day 28 and Day 35, phone follow-up for symptom assessment will be done.
 - m. Investigator will rate severity of clinical signs/symptoms of RSV in the CSS questionnaire based on participant interview by phone (or other digital call, if possible).
 - n. For all female participants of childbearing potential, a urine pregnancy test is to be performed on-site at screening and at Day 21.
 - o. Follicle stimulating hormone (FSH) will be tested at screening for female participants who are amenorrheic for 12 months or less.
 - p. Study site personnel will diagnose RSV locally for eligibility, using a study-specific bilateral nasal MT swab and a polymerase chain reaction (PCR)-based or other molecular-based diagnostic assay. They should ship the leftover specimen for any patient that is subsequently randomized. Collection of a study-specific bilateral nasal MT swab at screening is not required if a standard-of-care (SOC) diagnostic sample is collected within 24 hours of screening start and yields a positive RSV result using a molecular-based diagnostic assay.
 - q. A nasal MT swab should be collected from each nostril and both swabs should be put in the same universal transport medium tube (ie, a bilateral nasal MT swab sample). Only at times when sampling of both nostrils is not feasible, such as in case of bleeding in one nostril, one nasal MT swab should be collected from one nostril (ie, the non-bleeding nostril).
 - r. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the sample used for local RSV diagnosis, whichever comes first AND within a window of 72 hours of RSV sign/symptom onset.
 - s. First study intervention administration should occur as soon as possible, but no later than 4 hours after randomization. The day of first study intervention administration is defined Day 1. Dosing should occur approximately every 12 hours, but the second dose may be delayed or brought forward (by maximum 4 hours) if the nominal timing for this dose falls in the middle of the night. Thereafter, dosing follows a regular AM/PM schedule. The study intervention can be administered with/without food.

- t. Depending on the time of randomization/enrollment, participants will receive 1 dose (PM) or 2 doses (AM and PM) of study intervention on Day 1. For participants who receive only 1 dose of study intervention on Day 1 (PM), dosing should continue until the morning of Day 8 (AM) so that all participants receive 14 consecutive doses in total.
- u. On Day 1, study site personnel will hand-out to the participant all the required study intervention for dosing at home. Study site personnel will instruct participants on how to use and store study intervention for at home dosing.
- v. Clinical evaluation includes vital sign assessments (ie, body temperature, respiratory rate, pulse/heart rate, and peripheral capillary oxygen saturation [SpO₂]) and targeted physical examination assessments (ie, presence of wheezing or crackles/ronchi). It is recommended that the vital signs are assessed after the participant has rested for at least 15 minutes. Clinical evaluation also includes evaluation of the occurrence of adverse events (AEs), RSV-related complications, and need for medications (including antibiotics).
- w. Only performed if the screening assessment occurred >8 hours before anticipated first dosing.
- x. In case the first dose treatment is early in the morning, a second assessment should be performed in the evening.
- y. If the participant is not employed and neither is anyone who may help them, the Hours missed from Work Questions will not be asked at any point.
- z. Only applicable if clinically indicated to evaluate a participant's ongoing AE(s) or any clinically significant laboratory, vital sign or ECG abnormality identified on Day 21. (see also footnote^e).
- aa. Study site personnel should collect the predose nasal MT swab as close as possible and prior to first study intervention administration. Leftover study-specific (pre) screening nasal MT swab specimen can serve as baseline IF this screening sample: was collected within 8 hours prior to first dose, is appropriately stored AND is available in sufficient volume (volume is considered sufficient if no more than 600 µL from the original sample has been used for local RSV testing and the entire remainder of the original sample is available). However, when local RSV diagnosis was performed using a SOC sample, then this Day 1 predose sample is required to be collected in any case.
- bb. Leftover nasal samples may be used for-biomarker research at the discretion of the sponsor.
- cc. Bilateral nasal MT swabs will be taken preferably at approximately the same time as the predose sample taken on Day 1. During scheduled visits on Day 3, Day 8, Day 14 and Day 21, bilateral nasal MT swabs will be collected by a health care practitioner. On Day 2 and Day 5, bilateral nasal MT swabs are collected at home preferably by a health care professional and, only if not possible by a health care professional, by the participant (or his/her spouse, partner, relative, or other caregiver) after being properly trained by the investigator/study-site personnel. In case preferred by the participant, all bilateral nasal MT swabbing may also be performed at the site. Date and time of swabs collected at home need to be recorded. All participants will be given appropriate nasal MT swabs and universal transport medium (same supplies as those used to collect nasal samples at the sites) to collect nasal MT swabs. All swabs collected at home should be stored immediately between 2°C and 8°C (in the refrigerator) and brought to the site at the latest at the Day 3 and the Day 8 visit.
- dd. Return of ePRO device only applies if the device was provided to the participant by the site. Site staff will ensure return of the ePRO device is arranged for participants who have a phone visit at Day 35, and for any participants who discontinue/withdraw from the study.
- ee. ePRO completion compliance should be assessed daily by the study site personnel via the ePRO vendor portal. If scheduled assessments are missing from the prior day, the sites will contact the participant as soon as possible to identify reason for missing PRO and document reasons for missing PRO assessments in the eCRF based on discussion with the participant.
- ff. .
- gg. Systolic and diastolic blood pressure need to be measured sitting or supine (preferably the same position at each measurement) after at least 5 minutes of rest.
- hh. A complete physical examination (including height and body weight measurements) will be performed at screening. A targeted physical examination will be performed at the other site visits and includes evaluation of body weight (Day 21 only), the respiratory system, nose, ear, throat, and facial and neck lymph nodes.
- ii. 12-lead ECGs will be obtained at screening, Day 1, Day 3, Day 8, and Day 14. An ECG may be repeated at the discretion of the investigator to rule out erroneous readings or to confirm abnormal ECG findings. Presence of an abnormal QTcF interval should be confirmed by repeat ECG recording. ECGs will be obtained in a supine position after at least 5 minutes rest. Additional monitoring of ECG can be done (unscheduled visit), if needed in the opinion of the investigator based on the

overall clinical picture. If ECG was performed as part of SOC within approximately 48 hours prior to screening completion (ie, randomization) and the participant is clinically stable, this may be used in determining study eligibility.

- jj. ECG to be performed approximately 1 hour after administration of first study intervention.
- kk. Biochemistry blood samples at Day 8 and Day 21 will be taken, if possible, under fasted conditions (fasted for at least 10 hours).
- ll. Safety laboratory tests will be done for each participant. Samples for clinical laboratory assessments will be collected and analyzed at the central laboratory. Any values that indicate a potential safety concern will be assessed by the investigator and appropriate follow-up actions, including potential discontinuation from treatment, will be carried out.
- mm. Levels of potassium and magnesium to be determined by the local and by the central laboratory. In case of confirmed hypokalemia and/or hypomagnesemia at screening, or at any of the visits in the study period, the levels of potassium and magnesium should be corrected also taking into account any underlying condition and as soon as possible to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required. Documentation of correction of electrolyte levels and the corrective measures as indicated in Section 8.3.7.2 must be maintained. For confirmed hypokalemia of <2.5 mEq/ L and/or hypomagnesemia of < 0.9 mEq/ L, please see Section 7.1 for study intervention discontinuation guidance.
- nn. Urinalysis will be performed by the central laboratory and includes dipstick analysis, and if needed microscopic examination.
- oo. Blood samples (sparse sampling) for determination of plasma concentrations of rilematovir will be collected preferable 1 hour post the first dose, or just before the second dose administration on Day 1, predose and approximately 1 hour post dose (first or second dose) on Day 3, and at a random time point on Day 8 for all participants. The following information needs to be recorded on the requisition form: date and time of study intervention administration, date and time of PK blood sampling, time of meal if any in the time window of 2 hours before and 2 hours after study intervention administration on the day of PK sampling. Samples can be used for the determination of plasma concentrations of metabolites of rilematovir, excipients, protein binding, or endogenous markers for enzymes or transporters involved in the metabolism and distribution of rilematovir, at the discretion of the sponsor.
- pp. A blood sample will be collected at screening, Day 3, Day 8, and Day 21 for biomarker research, including but not limited to host RNA analysis. At screening, at Day 3, and at Day 21 an additional blood sample will be collected for protein analysis (eg, cytokines).
- qq. All AEs and serious AEs will be collected from signing of the main ICF onwards until the last follow-up visit (end of study visit). Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.
- rr. Medications taken will be discussed with the investigator and recorded on the concomitant medication page of the eCRF.

Notes:

1. Additional unscheduled visits in case of laboratory abnormalities, ECG abnormalities, need for clinical follow-up of (an) AE(s) can be scheduled at the discretion of the investigator.
2. See Appendix 10.20 for guidance on study conduct during the Coronavirus Disease 2019 (COVID-19) pandemic.
3. In case of supply issues for nasal MT swabs because of increased demand due to the COVID-19 pandemic, alternative nasal swabs instead of nasal MT swabs may be provided for nasal sample collection for the study assessments.

2. INTRODUCTION

Rilematovir (JNJ-53718678) is an investigational, potent small molecule respiratory syncytial virus (RSV) specific fusion inhibitor belonging to the indole chemical class. Rilematovir targets the RSV fusion protein and prevents the conformational changes of the F-protein required for fusion of the viral envelope with the host cell membrane and for cell-to-cell fusion, thereby inhibiting viral replication and syncytia formation. Rilematovir is currently in late phase development as treatment for RSV infection.

For the most comprehensive nonclinical and clinical information regarding rilematovir, refer to the latest version of the Investigator's Brochure (IB) for rilematovir ([IB 2020](#)).

The term "study intervention" throughout the protocol, refers to the administration of study intervention as defined in Section [6.1](#).

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Respiratory syncytial virus is a negative-stranded ribonucleic acid (RNA) virus belonging to the *Pneumoviridae* family, and is considered the most important cause of lower respiratory tract disease (LRTD) in infants, young children, and a common cause of acute respiratory disease in adults with the risk of severe infection increasing with age, as well as associated high-risk comorbidities ([Hall CB 2001](#), [Nair 2010](#)). Two subtypes of RSV have been identified, ie, subtypes A and B, that generally co-circulate simultaneously ([Falsey & Walsh 2000](#)). The RSV season occurs during winter months in regions with temperate climates in the Northern and Southern Hemispheres and throughout the year or with peaks semi-annually in tropical regions ([AAP 2006](#), [Bloom-Feshback 2013](#), [Yusuf 2007](#)).

The impact of RSV infections in adults is being increasingly recognized with the wider use of molecular testing of adult patients presenting with respiratory tract infections ([Nam and Ison 2019](#)). It has been estimated that RSV infects 3% to 10% of adults annually ([Wantuch 2014](#)). In the United States (US), an annual estimated 61,000-177,000 hospitalizations and 10,000-14,000 deaths are attributable to RSV in adults ≥ 65 years of age ([Falsey 2005](#)). Some of the factors that increase susceptibility to RSV in the elderly include declining immune system function such as lower RSV-specific serum immunoglobulin (Ig) and nasal IgA titers ([Falsey and Walsh 1998](#), [Walsh 2004](#)). In a longitudinal assessment over 12 RSV seasons in a single community (n=13,809), RSV was detected in 11% of outpatient adults ≥ 60 years of age with medically attended acute respiratory illness. The relative risk of a serious outcome (ie, hospitalization, emergency room visit, and pneumonia) was significantly increased in RSV-infected persons aged ≥ 75 years of age (versus 60-64 years of age) and in those with chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF) ([Belongia 2018](#)). The severity of adult RSV disease is likely

multifactorial involving age, immune factors, and comorbid conditions (Walsh 2004, Falsey 2019, Malloy 2013). While RSV typically presents in adults as self-limited upper respiratory tract disease (URTD) or LRTD, it is a significant cause of severe respiratory infection in elderly adults aged ≥ 65 years of age (Duncan 2009, Falsey 2005, Jain 2015) and in adults (regardless of age) with underlying cardiopulmonary comorbidities such as asthma, COPD, and CHF (Duncan 2009, Falsey 2005, Falsey 2019). These patients may present primarily with symptoms of decompensated heart failure or acute exacerbation of COPD. Among elderly adults who are at risk for severe RSV disease, RSV infection may manifest as severe or life-threatening LRTD with pneumonia, a requirement for ventilatory support, and short- and long-term morbidity (Tseng 2020).

Current treatment options for RSV are generally supportive in nature, consisting of supplemental oxygen, intravenous fluids, and bronchodilators. No vaccines or antivirals have been approved for the prevention or treatment of RSV infection in adults. Aerosolized, oral, and intravenous ribavirin have been used selectively in RSV-infected immunocompromised adults with variable results (Nam and Ison 2019). Due to the significant disease burden and the lack of effective treatment, the unmet medical need (prophylactically and therapeutically) is substantial, especially related to antiviral treatment in the high-risk adult population as described above.

Rilematovir is being developed for the treatment of adult patients who are at high risk of RSV-related disease progression and thus are considered to have a high unmet medical need. Early antiviral treatment of RSV infection in an outpatient setting may offer the potential to resolve the infection sooner and prevent or halt the progression to severe RSV disease and RSV-related complications.

Data from the non-hospitalized adult Phase 2a study 53718678RSV2004 indicate a trend towards a favorable effect of rilematovir 80 mg and 500 mg (dosed as once daily for 7 days) compared to placebo. In addition, the median time to resolution of Key RSV Symptoms (ie, cough, wheezing, coughing up phlegm [sputum], short of breath, fatigue, and feverishness) assessed by participants using the respiratory infection (RI) patient reported outcome (PRO) or Respiratory Infection Intensity and Impact Questionnaire [RiiQ]) in the subgroup of participants with ≤ 3 days since symptom onset was shorter in rilematovir 80 mg group (7.6 days) and rilematovir 500 mg group (8.0 days, 32% reduction compared to placebo) as compared to the placebo group (11.8 days).

In consideration of the unmet medical need in adults who are at high risk of severe RSV disease, this Phase 2b study will evaluate efficacy, safety, and tolerability of rilematovir compared to placebo in high-risk adults in an outpatient setting, presenting with symptoms consistent with at least 2 LRTD symptoms, one of which needs to be at least moderate or worsened in case the participant had pre-existing LRTD symptoms and who are randomized within a window of 72 hours since RSV symptom onset. High risk in this study is defined as elderly adults (≥ 65 years of age), or adults (≥ 18 to ≤ 65 years of age) with underlying high-risk comorbid cardiopulmonary conditions (COPD, asthma, or CHF). The study will be stratified at randomization by the following factors: high-risk (< 65 years of age with underlying high-risk comorbid cardiopulmonary conditions [COPD, asthma, or CHF] versus ≥ 65 years of age without underlying high-risk

conditions versus ≥ 65 years of age with underlying high-risk comorbid cardiopulmonary conditions) and time since symptom onset (≤ 48 hours versus > 48 -72 hours).

Data from this Phase 2b outpatient Study 53718678RSV2008 in high-risk adults will provide guidance for the design of confirmatory Phase 3 studies.

2.2. Background

Enveloped viruses like RSV have a complex membrane-fusion machinery that includes a fusion protein that enables the deposition of the viral nucleic acid genome into the host cells and initiates their replication (Colman and Lawrence 2003, Leung 2005). Rilematovir is an investigational RSV-specific fusion inhibitor belonging to the indole chemical class and is currently in development for the treatment of RSV infection in both adult and pediatric populations. Rilematovir has demonstrated in vitro activity against a panel of viruses belonging to both the RSV subfamilies A and B. In addition, trends for antiviral activity and clinical benefit of rilematovir were demonstrated during clinical studies in healthy adults inoculated with RSV (Study 53718678RSV2001), in non-hospitalized adult participants naturally infected with RSV (Study 53718678RSV2004), and in naturally RSV-infected hospitalized pediatric participants (Study 53718678RSV1005 and Study 53718678RSV2002). For the most comprehensive nonclinical and clinical information regarding rilematovir, refer to the latest version of the IB for rilematovir (IB 2020).

Nonclinical Studies

Rilematovir has been extensively evaluated and characterized in both in vitro and in vivo pharmacological, pharmacokinetic (PK), and toxicological studies. These nonclinical in vitro and animal in vivo efficacy data demonstrate that rilematovir is a selective and potent small molecule RSV fusion inhibitor, capable of significantly reducing the viral titer in preclinical RSV models. Concurrently, a decrease of the virus-induced pro-inflammatory response was observed in RSV-infected and rilematovir-treated Balb/C mice and neonatal lambs. No in vitro antiviral activity was observed for the rilematovir minor metabolites M12 (JNJ-53541683), M19 (JNJ-64564071), and M37 (JNJ-69101045), while activity was observed for M5 (JNJ-54172794) which was lower than the activity observed for rilematovir. Detailed results of performed nonclinical studies are described in the latest IB for rilematovir (IB 2020).

Clinical Studies

Human Pharmacokinetics and Product Metabolism

In the single-dose escalation part of Study 53718678RSV1001, the mean maximum plasma concentration (C_{\max}) of rilematovir increased proportionally with dose after administration of rilematovir doses between 25 mg and 1,000 mg under fasted conditions. Mean AUC from time of administration extrapolated to infinity ($AUC_{0-\infty}$) of rilematovir increased slightly more than dose-proportionally with increasing rilematovir dose from 25 mg to 1,000 mg. Median time to reach C_{\max} (t_{\max}) was 1 hour, except for the 1,000 mg dose group, in which it was 2.5 hours. Similarly, mean apparent terminal elimination half-lives ($t_{1/2\text{term}}$) for the different dose groups were

observed. Based upon data from Study 53718678RSV1004 in healthy Japanese adult men and Study 53718678RSV1001, C_{\max} and $AUC_{0-\infty}$ for rilematovir were similar between Caucasian and Japanese participants.

In the multiple dose escalation part of Study 53718678RSV1001 in adult participants under fed conditions, predose plasma concentrations (C_{trough}) reached steady state after 1 day of treatment with rilematovir. On Day 8, rilematovir exposure expressed as mean C_{trough} , minimum plasma concentration (C_{\min}), C_{\max} and AUC from time of administration up to 24 hours post dosing (AUC_{0-24h}) demonstrated a dose-proportional increase with increasing rilematovir dose from 250 mg every 24 hours (q24h) to 500 mg q24h. Fluctuation was lower for the 250 mg twice daily regimen compared with the 500 mg once daily regimen. For the 500 mg q24h dose group, mean C_{24h} values of rilematovir were similar between Day 1 and Day 8, while C_{\max} and AUC_{0-24h} were 1.15- and 1.16-fold higher at Day 8. For the 250 mg every 12 hours (q_{12h}) dose group, mean C_{12h} , C_{\max} and AUC from time of administration up to 12 hours post dosing (AUC_{0-12h}) of rilematovir were increased 1.53-, 1.42-, and 1.53-fold, respectively, on Day 8 compared with Day 1. The mean total amount of rilematovir excreted in urine over the dosing interval at steady state was low; mean renal clearance was very low, and similar between dose regimens.

In study 53718678RSV2001 in adult participants, the PK profile of rilematovir at multiple doses of 75 mg, 200 mg, and 500 mg once daily for 7 days was evaluated in healthy adult participants inoculated with RSV-A Memphis 37b virus. The PK results from this study were consistent with those from corresponding regimens in Study 53718678RSV1001, indicating that viral infection did not affect the PK of rilematovir.

Results from the mass balance Study 53718678RSV1008 demonstrated that rilematovir was the major circulating entity in plasma (44% to 47%), with M12 and M37 being the most abundant metabolites at 17-22% and 9.73% of AUC from time of administration up to 96 hours post dosing (AUC_{0-96h}) of total radioactivity (TR), respectively; M19, M5, and glucuronide metabolites (M8 and M9) represented 5%, 4%, and 1% (each), respectively. Most of TR was recovered in feces (71%) and urine (20%), with unchanged drug representing 10% to 16% and 1%, respectively.

A population PK (popPK) model for rilematovir has been developed using data from Study 53718678RSV1001 in healthy adults. The PK results from the study part evaluating the oral suspension in Study 53718678RSV1007, indicated similar bioavailability of the oral suspension compared to the oral solution formulation, with a relative bioavailability of 109% (C_{\max}) and 104% (AUC).

Results from Study 53718678RSV2004 in RSV-infected adult patients demonstrate that the popPK model provides an adequate description of the majority of the data, although with higher than expected levels for C_{trough} , C_{\max} , and AUC_{0-24h} . The mean standard deviation (SD) Day 7 AUC_{0-24h} and C_{trough} following administration of 500 mg rilematovir in this study (N=16) were 38,800 (16,600) ng.hr/mL and 698 ng/mL (546), respectively, compared to 26,520 (7,520) ng.hr/mL and 334 (197) ng/mL, respectively, observed in Study 53718678RSV2001 (N=17). The mean (SD) Day 1 and Day 7 AUC_{0-24h} and C_{trough} following administration of 80 mg rilematovir in this study (N=16) were 4,190 (987) and 5,820 (2,360) ng.hr/mL and 67.6 (40.9) and

101 (82.2) ng/mL, respectively. The mean (SD) Day 1 and Day 7 AUC_{0-24h} and C_{trough} following administration of 500 mg rilematovir in this study (N=16) were 27,600 (7,550) and 38,800 (16,600) ng.hr/mL and 454 (270) and 698 (546) ng/mL, respectively. The Day 7 exposure was therefore higher than in Study 53718678RSV2001. The mean (SD) Day 1 and Day 7 C_{max} after 80 mg rilematovir were 399 (58.9) ng/mL (N=23) and 498 (89.9) ng/mL (N=20), respectively, and 2,500 (426) ng/mL (N=17) and 3,150 (800) ng/mL (N=16), respectively, after 500 mg rilematovir.

Effect of Food

In Study 53718678RSV1001, mean C_{max} of rilematovir was approximately 35% lower and median t_{max} increased from 1 hour to 3.5 hours when rilematovir was administered under fed conditions compared with fasted conditions. Mean $AUC_{0-\infty}$ of rilematovir was slightly lower (93%) when rilematovir was administered under fed conditions compared with fasted conditions. The PK results from the study part evaluating a single dose (500 mg) of the oral suspension in Study 53718678RSV1007, demonstrated that $AUC_{0-\infty}$ and C_{max} of rilematovir were 5% and 35%, respectively, lower when the oral suspension was administered under fed conditions compared to fasted conditions. The mean fed/fasted ratio was 95% for $AUC_{0-\infty}$. Therefore, rilematovir can be taken with or without food.

Bioavailability of the Rilematovir Oral Suspension and Oral Film-Coated Tablet.

The interim PK results from Study 53718678RSV1007, demonstrated similar bioavailability of several oral concept suspension formulations compared to the oral solution formulation.

The PK results for the oral suspension G001 demonstrated similar bioavailability compared to the oral solution formulation (G024), with a relative bioavailability of ~109% (C_{max}) and ~104% (AUC) under fasted conditions and a relative bioavailability of ~65% (C_{max}) and ~95% (AUC_{inf}) under fed conditions.

The PK results for the oral suspension reconstituted from powder G015 (concept formulation) and solvent G010 demonstrated similar bioavailability compared to the oral solution formulation (G024), with a relative bioavailability of ~110% (C_{max}) and ~99% (AUC) under fasted conditions and a relative bioavailability of ~57% (C_{max}) and ~100% (AUC) under fed conditions.

The interim PK results from Study 53718678RSV1011 demonstrated similar bioavailability of the oral solid concept formulation compared to the oral suspension formulation (provided as powder G007 + solvent G005). In part 1 of Study 53718678RSV1011, a new oral solid concept formulation of rilematovir was evaluated in a 3-way crossover design for assessment of the bioavailability relative to the oral suspension (G007 powder + G005 solvent) and food effect in 24 healthy adult participants.

The PK results for the oral solid concept formulation G033 demonstrated similar bioavailability compared to the oral suspension formulation (G007 powder + G005 solvent), with a relative bioavailability of ~91% (C_{\max}) and ~98% (AUC) under fasted conditions and a relative bioavailability of ~72% (C_{\max}) and ~94% (AUC) under fed conditions. The ~30% reduction in C_{\max} under fed conditions for the solid concept formulation is similar to the food effect with the oral suspension (33-43% reduction; analyzed in Parts 6 & 7 of Study 53718678RSV1007).

The oral solid concept G033 is the formulation to be administered in this study, further referred to as oral film-coated tablet.

Drug-Drug Interactions

Based on in vitro data, rilematovir is a cytochrome P450 (CYP)2B6 inducer, a substrate but not an inhibitor of P glycoprotein (P-gp) and breast cancer resistance protein up to 15 μM , and an inhibitor of organic anion transporting polypeptide (OATP)1A2, OATP1B1, organic anion transporter 3, organic cation transporter (OCT)1, and OCT2. In vivo clearance of rilematovir will likely not be hepatic uptake-limited or sensitive to interactions with hepatic uptake inhibitors.

The potential effect of rilematovir on the PK of sensitive CYP substrates was evaluated in the drug-drug interaction Study 53718678RSV1002. In this study, the drug interaction potential of rilematovir was evaluated at a dose level of 500 mg on a drug cocktail containing selective CYP probes (CYP3A4 [midazolam], CYP1A2 [caffeine], CYP2C9 [warfarin]), and a non-selective P-gp substrate (fexofenadine). In this study, participants received rilematovir 500 mg once daily for a total of 13 consecutive days. Results of this study suggested a weak inhibition of CYP3A4 activity in the presence of a single dose of rilematovir and a weak induction of CYP3A4 activity after repeated administration of rilematovir. Overall, at steady state of rilematovir, the exposure of midazolam is hardly affected by rilematovir due to the combined CYP3A4 inhibitory and inductive effect described. In Study 53718678RSV1002, rilematovir had no clinically significant effect on CYP2C9 and CYP1A2. Single and multiple doses of rilematovir reduced the plasma exposure of fexofenadine. The observed decrease in exposure of fexofenadine after coadministration of a single dose of rilematovir is due to the inhibition of OATP1A2, an uptake transporter located in the gut; further reduction of the fexofenadine exposure after repeated dosing of rilematovir, was likely due to induction of P-gp. Please see Section 6.8 for prohibitions related to concomitant use of specific inhibitors or inducers of CYP3A4 enzymes.

In Study 53718678RSV1006, rilematovir was coadministered with itraconazole (a strong CYP3A4 and P-gp inhibitor) and with rifampicin (an inducer of CYP3A4, glucuronyl transferase, and P-gp, and an inhibitor of OATP). $\text{AUC}_{0-\infty}$ of rilematovir increased approximately 3-fold upon coadministration with itraconazole 200 mg once daily. After coadministration of rilematovir with a single dose of rifampicin, no significant change in the total exposure of rilematovir was observed, suggesting the OATP transporter is not involved in the disposition of rilematovir. However, repeated administration of rifampicin 600 mg once daily decreased the exposure of rilematovir, primarily due to induction of CYP3A4.

Efficacy

In a challenge model for RSV infection in healthy adults (Study 53718678RSV2001), exposure to rilematovir resulted in a reduction of viral load over time in all rilematovir dose groups (75 mg, 200 mg, and 500 mg) as compared to the placebo group with no clear dose-response for the active groups. This was associated with lower clinical symptom scores and mucus production.

The Phase 2 pilot Study 53718678RSV2004 explored the antiviral activity, clinical outcomes, safety, tolerability, and PK of rilematovir at two dose levels (80 and 500 mg q.d for 7 days) in non-hospitalized adult participants (with or without high-risk conditions for RSV-related disease progression) naturally infected with RSV.

There were 72 participants randomized and dosed, of whom 66 (91.7%) had PCR-confirmed RSV infection at baseline, comprising the intent-to-treat-infected (ITT-i) analysis set. Results of this study in adult non-hospitalized RSV-infected participants demonstrated an improvement in clinical course of RSV disease:

- No clear effect of rilematovir 80 mg and 500 mg versus placebo was observed on RSV viral load over time in both mean nasal RSV RNA viral load AUC and change from baseline analyses. However, from Day 2 through Day 8, the proportion of participants with undetectable RSV RNA viral load was higher in the rilematovir 500 mg group compared to the rilematovir 80 mg group and the placebo group. At Day 8 (end of treatment phase), 81.3% of participants in the rilematovir 500 mg group had undetectable RSV RNA by quantitative reverse transcription polymerase chain reaction (qRT-PCR), compared to 42.1% and 47.4% in the rilematovir 80 mg and placebo groups, respectively. The time to first confirmed undetectable nasal RSV RNA was favorable for the rilematovir 500 mg group; the median Kaplan-Meier (KM) estimate was 5.9 days in the rilematovir 500 mg group, 8.0 days in the rilematovir 80 mg group, and 7.5 days in the placebo group. In general, a similar trend was observed in the subgroup of participants with ≤ 3 days since symptom onset.
- The overall median KM estimate for time to resolution of key RSV Symptoms (ie, cough, wheezing, coughing up phlegm (sputum), short of breath, fatigue, and feverishness assessed by participants using RiiQ was 7.6 days in the rilematovir 80 mg group, 7.1 days in the rilematovir 500 mg group, and 9.6 days in the placebo group. The median KM estimate in the subgroup of participants with ≤ 3 days since symptom onset was 7.6 days in the rilematovir 80 mg group, 8.0 days in the rilematovir 500 mg group, and 11.8 days in the placebo group. The median KM estimate in the subgroup of participants with >3 to 5 days since symptom onset was 8.5 days in the rilematovir 80 mg group, 5.1 days in the rilematovir 500 mg group, and 5.0 days in the placebo group.

Overall, data from this study indicate a trend towards a favorable effect of rilematovir 80 mg and 500 mg (dosed once daily for 7 days) compared to placebo, especially in the subgroup of participants ≤ 3 days since symptom onset. In addition, the median time to resolution of Key RSV

Symptoms in the subgroup of participants with ≤ 3 days since symptom onset was shorter after rilematovir 80 mg and 500 mg treatment compared to placebo.

Trends in benefits for clinical course outcomes and antiviral effects were observed in interim analyses of a study in RSV-infected pediatric participants. For more details, refer to the latest version of the IB for rilematovir ([IB 2020](#)).

Safety and Tolerability

Based on the available clinical data, no adverse events (AEs) or clinically significant laboratory abnormalities, abnormalities in vital signs parameters, electrocardiogram (ECG) abnormalities, or physical examination findings indicative of a safety concern have been identified.

Study 53718678RSV1009

In Study 53718678RSV1009, the effect of rilematovir on the cardiac repolarization interval in healthy adult participants was evaluated with dosing up to 4,500 mg. Part 1 of the study was the dose escalation part; based on the PK and safety results of Part 1, the suprathreshold dose of 4,500 mg was selected for Part 2 of the study, the thorough QT (TQT) part. Exposure-response analysis was performed to determine the relationship between the concentrations of rilematovir and QT/QTc interval changes extracted from Holter monitor ECG data. Based on this analysis, an important potential risk of QT interval prolongation was identified for rilematovir. The model-predicted mean placebo-corrected change from baseline for the individual-corrected QTc ($\Delta\Delta\text{QTcI}$) (90% confidence interval [CI]) at the observed geometric mean of the C_{\max} of the effect compartment concentration following a single dose of 500 mg (2,165 ng/mL) and 4,500 mg (10,153 ng/mL) rilematovir was 4.8 ms (4.2; 5.3 ms) and 20.3 ms (18.2; 22.3 ms), respectively. The highest C_{\max} at the effect compartment following a single dose associated with an upper limit of the 90% CI for $\Delta\Delta\text{QTcI} < 10$ ms was 4,350 ng/mL, which corresponds with approximately a single dose of 1,000 mg. Based on exposure-response analysis, an important potential risk of QT interval prolongation was identified for rilematovir. For more details on the analysis, refer to the latest version of the IB for rilematovir ([IB 2020](#)). A change to a twice daily dosing regimen and several other mitigation measures to safeguard the participants have been implemented.

Study 53718678RSV1009 demonstrated that a single dose of rilematovir was generally safe and well tolerated in healthy adult participants. No clinically significant safety findings were identified in any participants dosed under fasted conditions with rilematovir, including the suprathreshold dose of 4,500 mg. In addition, there were no cardiac AEs and no clinically significant changes in vital signs, ECG, or laboratory abnormalities. No deaths, SAEs, AEs of at least Grade 3, or AEs leading to discontinuation of study treatment were observed. Among participants who received 2,000 mg, 3,000 mg, and 4,500 mg doses of rilematovir, 50.0%, 83.3%, and 83.3%, respectively, experienced at least 1 AE as compared to 55.6% of participants who received placebo. Diarrhea, nausea, and headache were more frequently observed in participants who received rilematovir compared to participants who received placebo.

An AE leading to early study termination was reported for 3 participants:

- One participant was reported with prolonged QT interval corrected using Fridericia's formula (QTcF) (>450 to ≤ 480 ms), based on findings from the safety ECG, during rilematovir (4,500 mg) treatment period, which was considered moderate in severity and probably related to the study agent. The AE resolved the same day.
- One participant was reported with the AEs vomiting, nausea, and headache during the 4,500 mg rilematovir treatment period. The AEs vomiting and nausea were considered mild in severity and possibly related to the study agent. The AE headache was considered mild in severity and doubtfully related to the study agent. A second event of vomiting was reported on the same day and was considered moderate in severity and possibly related to the study agent. These AEs resolved the same day.
- One participant was reported with a skin reaction during the 400 mg moxifloxacin treatment period. This AE was considered mild in severity and possibly related to the study agent. The AE resolved the same day.

At least 1 AE was reported in 12 (52.2%) participants after receiving 500 mg rilematovir, 22 (88.0%) participants after receiving 4,500 mg rilematovir, 9 (39.1%) participants after receiving placebo, and 12 (50.0%) participants after receiving 400 mg moxifloxacin. During the treatment phase, diarrhea, nausea, and headache were more frequently observed in participants who received 4,500 mg of rilematovir compared to participants who received 500 mg of rilematovir, placebo, or 400 mg of moxifloxacin.

Mean changes in safety ECG parameters were generally minor, and none of them were considered clinically relevant except for 1 event of prolonged QTcF in 1 participant, which was reported as AE and led to study discontinuation (see above).

Study 53718678RSV2001

Study 53718678RSV2001 evaluated the antiviral activity, safety, and PK of rilematovir against RSV infection in the RSV challenge model in healthy adult participants. Overall, the oral solution formulation was generally safe and well tolerated. No SAEs or deaths were reported during the study. No treatment-emergent adverse events (TEAEs) with severity Grade 3 or higher were observed during the treatment phase. During follow-up, 1 participant in the placebo group was reported with a Grade 3 increased lipase, which was reported as an AE. Three participants permanently discontinued the study due to a TEAE: 2 participants were reported with an ECG change (one Grade 2 AE [abnormally high QRS duration, QRS = 126 ms] in the 75 mg rilematovir group and one Grade 1 AE [no specific change] in the 200 mg rilematovir group) and 1 participant (placebo group) was reported with a Grade 2 AE urticaria.

Eight (53.3%) participants in the 75 mg rilematovir group, 13 (76.5%) participants in the 200 mg rilematovir group, 13 (72.2%) participants in the 500 mg rilematovir group, and 9 (56.3%) participants in the placebo group were reported with at least one TEAE during the treatment phase, which were all either Grade 1 or Grade 2 in severity. The most frequently reported TEAEs (>2 participants in any treatment group) during the treatment phase were diarrhea, increased blood

cholesterol, increased low density lipoprotein, and epistaxis. For diarrhea there was a trend for dose relationship. However, it was also observed in the placebo-treated group and was considered related to the amount of 2-hydroxypropyl-beta-cyclodextrin (HP- β -CD) (both rilematovir and placebo solutions contain 30% HP- β -CD as an excipient) administered, which is a known emollient and has been correlated with increased incidences of diarrhea as main AE.

ECG abnormalities were infrequently reported, and results were generally consistent with those observed in the pooled Phase 1 studies. Graded and non-graded laboratory abnormalities were generally consistent with those observed in the pooled Phase 1 dataset.

Altogether, rilematovir was generally safe and well tolerated. No relation was noted between the incidence of AEs and the dose level and/or the dose regimen of rilematovir. No safety signal was identified.

Study 53718678RSV2004

Results from Study 53718678RSV2004 demonstrated that rilematovir was generally safe and well tolerated in RSV-infected non-hospitalized adults. No new safety signal was identified.

There were no deaths, no treatment-emergent (S)AEs, and no AEs of severity Grade 3 or 4 in the study, except for 1 (4.2%) participant in the placebo group, who was reported with an AE of severity Grade 3 (bacterial infection). Overall, 37.5%, 75.0%, and 62.5% of participants in the rilematovir 500 mg group, in the rilematovir 80 mg group, and in the placebo group, respectively, experienced at least 1 TEAE, of which diarrhea was the most frequently reported TEAE. This AE occurred at similar incidences in all treatment groups and at similar incidences as observed in earlier studies with the same oral solution. This is likely due to the hydroxypropyl- β -cyclodextrin content (30%) in the oral solution used in this trial for both active and placebo. The oral suspension formulation used in ongoing and future trials does not contain this excipient. Six participants discontinued study intervention prematurely due to the following AEs: diarrhea (1 participant in the placebo group and 3 participants in the rilematovir 500 mg group, of whom 2 also discontinued study participation), abdominal discomfort (1 participant in the rilematovir 80 mg group), and urticaria (1 participant in the rilematovir 80 mg group).

ECG abnormalities were infrequently reported. No cardiac safety signal was identified. Graded and non-graded laboratory abnormalities and vital signs observations were generally consistent with those observed in the pooled Phase 1 dataset.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of rilematovir can be found in the current IB ([IB 2020](#)).

2.3.1. Risks for Study Participation

2.3.1.1. Known risks

No formal adverse drug reaction analysis has yet been conducted for rilematovir. No adverse drug reactions or known risks associated with rilematovir have been identified.

2.3.1.2. Potential risks

All therapies have the potential to cause adverse drug reactions.

According to the latest IB update, a total of 345 adult participants and 192 pediatric participants received at least 1 dose of rilematovir. Of the 345 adult participants, 251 received at least one dose of rilematovir ≥ 500 mg. In total, 92 pediatric participants received multiple ≥ 500 mg adult dose equivalents (IB 2020).

Please refer to Section 2.2 for details on the reported AEs and laboratory/ECG abnormalities in the studies conducted to date.

Based upon the available clinical data, no risk related to the hepatobiliary system was identified. However, given the hepatobiliary-related nonclinical findings and because the amount of clinical data are limited, the sponsor considers hepatobiliary effects to be a safety topic of special interest and hepatobiliary function will be monitored by routine hepatic function tests during clinical studies.

In the TQT Study 53718678RSV1009 (healthy adults), the important potential risk of QT interval prolongation with rilematovir administration was identified after administration of the 4,500 mg supratherapeutic dose. Based on exposure-response analysis, with a single dose of 1,000 mg rilematovir the QTc interval prolongation is predicted to remain below the 10 msec threshold of regulatory concern;(see Section 2.2 and the IB [IB 2020]) for more information). The dose regimen (see Section 4.3) for this study was selected in consideration of this potential risk. Several other measures to safeguard the participants (see Section 2.3.3) have also been implemented

Overall, the oral suspension formulation used in Part 1 and 2 of the TQT study was generally safe and well tolerated in healthy adult participants. Most AEs were mild, with diarrhea being the most frequently reported AE. No Grade 3 or 4 AEs were reported during this study. From a clinical safety perspective, no clinically relevant ECG abnormalities (related to QTcF or other) or cardiovascular AEs were observed in this study.

Available clinical safety data do not indicate any safety signal or concern with regard to the cardiovascular system (Section 2.2).

Study procedures such as blood sampling carry a potential risk (eg, pain, discomfort, hematoma) to the participant.

The evaluation of rilematovir antiviral activity and sequencing requires bilateral nasal mid-turbinate swabbing. However, this is a minimally invasive assessment that at most results in

some short-term discomfort for the participant and is usually well tolerated, though occasionally nasal bleeding can occur. Examples of other AEs that may occur, but are not considered severe, are coughing, gagging, nausea, and vomiting.

2.3.2. Benefits for Study Participation

2.3.2.1. Known benefits

Proof-of-concept antiviral effect was established in adult healthy volunteers challenged with a laboratory strain of RSV (Study 53718678RSV2001) (Section 2.2).

In the ongoing pediatric Study 53718678RSV2002, the interim analysis (data cut-off 02 January 2020) data demonstrated a trend towards an antiviral effect of rilematovir in hospitalized children ≥ 28 days of age and ≤ 3 years of age with RSV disease compared to placebo, with more pronounced effects in the subgroup with symptom onset ≤ 3 days compared to the subgroup with symptom onset > 3 -5 days to randomization.

In the adult Study 53718678RSV2004, the interim analysis (data cut-off 23 September 2019) data demonstrated positive trends for time to first confirmed RSV undetectability for rilematovir compared to placebo. Effects appeared greater in the subgroup of participants with symptom onset ≤ 3 days compared to the subgroup with symptom onset > 3 -5 days to randomization.

However, the clinical benefit of this compound remains to be established.

2.3.2.2. Potential benefits

An increasing age (elderly; ≥ 65 years of age or more) and/or the presence of underlying high-risk cardiopulmonary comorbidity (COPD, asthma, or CHF) have been clearly defined as high-risk factors for severe illness and hospitalizations in RSV-infected adults. The high-risk adults participating in this study may have a benefit regarding the clinical course of their RSV infection. Treatment with rilematovir could reduce the severity and duration of RSV signs and their impact on functioning, reduce the effect of RSV infection on physiologic parameters, reduce the risk of progression to more severe disease and complications, reduce the need for and duration of supportive care (eg, oxygen supplementation), and accelerate the participants' return to pre-RSV health status.

Study intervention will be provided in addition to, not in replacement of, standard-of-care (SOC) supportive and symptomatic therapy.

In Study 53718678RSV2004, data demonstrated a positive trend for time to symptom resolution of key RSV Symptoms for rilematovir compared to placebo. Effects appeared greater in the subgroup of participants with symptom onset ≤ 3 days compared to the subgroup with symptom onset > 3 -5 days to randomization.

In the ongoing pediatric Study 53718678RSV2002, the interim analysis (data cut-off 02 January 2020) data demonstrated a trend towards an improvement in the clinical course of RSV disease in children ≥ 28 days and ≤ 3 years of age with RSV disease of rilematovir compared to

placebo, with more pronounced effects in the subgroup with symptom onset ≤ 3 days compared to the subgroup with symptom onset > 3 -5 days to randomization.

2.3.3. Benefit-Risk Assessment for Study Participation

Currently the only available treatment for RSV in immunocompetent adults is supportive and symptomatic care (see Section 2.2). Based on the available data and proposed safety measures, the overall risk/benefit assessment for this study is acceptable for the following reasons:

- Antiviral effect proof-of-concept was established in adult healthy volunteers challenged with a laboratory strain of RSV (study 53718678RSV2001) and in RSV-infected pediatric participants (study 53718678RSV1005). Additionally, data from an interim analysis of Study 53718678RSV2002 in RSV-infected pediatric participants showed benefits for clinical course outcomes and antiviral effects (Section 2.2).
- Data from the 53718678RSV2004 analysis in adult outpatients showed a trend for an antiviral effect as well a trend to improvement in the RSV clinical course outcomes (Section 2.2).
- No safety concerns were identified in Study 53718678RSV2004 in non-hospitalized adult participants infected with RSV (Section 2.2).
- No safety concerns were identified in studies in RSV-infected pediatric participants (Study 53718678RSV1005 in children > 1 month to ≤ 24 months of age and from an interim analysis of Study 53718678RSV2002 in children ≥ 28 days and ≤ 3 years of age) (Section 2.2).
- No safety concerns were identified in completed studies in adult healthy volunteers to date and most observed AEs and laboratory abnormalities were mild to moderate in severity and considered not related to rilematovir by the investigator (Section 2.2).
- Several safety measures have been proposed to minimize potential risk to participants, including:
 - Only participants who meet all eligibility criteria (as specified in the protocol, Sections 5.1 and 5.2) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of the participants in the study.
 - Utilization of study intervention discontinuation and withdrawal criteria specific to QTcF interval changes (see Section 7.1 and 7.2).
 - Safety surveillance in this study will monitor standard safety parameters associated with investigational drug development (see Section 8.2) and safety topics of interest for rilematovir (see Section 8.3.6) as part of the study assessments.
 - Utilization of results from diagnostic testing (swab) performed as part of SOC.
 - The establishment of an Independent Data Monitoring Committee (IDMC) (see Section 9.6) to monitor data on a regular basis to ensure continuing safety of the participants enrolled in this study (see Sections 8.2 and 8.3).
- In view of the identified important potential risk of QT interval prolongation (see Section 2.2, TQT Study 53718678RSV1009), the following measures have been implemented to minimize the potential risk to participants:

- The selection of the 250 mg twice daily dose regimen which, relative to the respective once daily dose regimens for which no safety concern was identified, will minimize C_{\max} while still maintaining AUC and increasing C_{trough} (see Section 4.3). For participants co-administered with moderate or strong CYP3A4 inhibitors (with the exception of posaconazole and ketoconazole), the dose will be reduced to 125 mg twice daily (see Sections 4.3, 6.1, 6.5 and 6.8).
- Specific cardiovascular and ECG-based criteria for eligibility assessment (see Section 5.1 and 5.2).
- Close monitoring of the use of concomitant medications will be conducted regularly (see Section 6.8).
- Regular ECG monitoring will be performed at screening and several timepoints during the study, including an ECG around t_{\max} on Day 1 and Day 3 (steady state). Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period. Further, unscheduled ECG assessments/visits can be performed based on the overall clinical picture as per the investigator's clinical discretion (see Schedule of Activities and Section 8.3.7.2).
- Close monitoring of potassium and magnesium will be done. Levels of potassium and magnesium will be determined by the local as well as the central laboratory. In case of confirmed hypokalemia and/or hypomagnesemia at screening, or at any of the visits in the study period, the levels of potassium and magnesium should be corrected also taking into account any underlying condition and as soon as possible to prevent cardiac disturbances (see Section 8.3.7.2). Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required. Documentation of correction of electrolyte levels and the corrective measures as indicated in Section 8.3.7.2 must be maintained. For confirmed hypokalemia of <2.5 mEq/ L and/or hypomagnesemia of <0.9 mEq/ L, participant study intervention will be discontinued (Section 7.1)
- Specific toxicity management for confirmed QTcF interval value ≥ 500 ms (see Section 8.3.7.2).
- Close follow-up of ECG- and cardiac-related AEs as part of medical monitoring.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with rilematovir are justified by the anticipated benefits that may be afforded to adult participants with RSV who are at high risk for RSV-related disease progression.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> • To evaluate efficacy of rilematovir compared to placebo with respect to the time to resolution of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) symptoms. 	<ul style="list-style-type: none"> • Time to resolution of RSV LRTD symptoms (ie, cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the participant using the Respiratory Infection

Objectives	Endpoints
	<p>Intensity and Impact Questionnaire (RiiQ™ Symptom Scale).</p> <p>Definition of resolution in participants without pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> - <i>All LRTD symptoms in the RiiQ Symptom Scale^a scored as 'None' (score = 0) or 'Mild' (score = 1) for at least 24 hours.</i> <p>Definition of resolution in participants with pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> - <i>Pre-existing symptoms that were worse at baseline should have improved at least 1 point on the RiiQ Symptom Scale from baseline for at least 24 hours; and</i> - <i>Pre-existing symptoms that were not worse at baseline should have not worsened from baseline severity for at least 24 hours; and</i> - <i>Symptoms that were not pre-existing at baseline should be scored as 'None' (score = 0) or 'Mild' (score = 1) on the RiiQ Symptom Scale for at least 24 hours.</i>
Secondary	
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir compared to placebo with respect to the incidence of post-baseline RSV-related complications. 	<ul style="list-style-type: none"> • Proportion of participants with post-baseline complications (ie, RSV-related pulmonary and extrapulmonary complications). <ul style="list-style-type: none"> - Pulmonary complications: primary viral pneumonia, bronchitis, respiratory failure, secondary bacterial pneumonia, and exacerbations of underlying chronic pulmonary diseases (such as chronic obstructive pulmonary disease [COPD] and asthma). - Extrapulmonary complications: cardiovascular and cerebrovascular disease events, CHF or exacerbation of underlying CHF, acute exacerbation of chronic kidney disease, severe dehydration, decompensation of

^a The RiiQ Symptom scale is a four item scale (0: no symptoms, 1: mild symptoms, 2: moderate symptoms, 3: severe symptoms).

Objectives	Endpoints
	previously controlled diabetes mellitus, and other airway infections (eg, sinusitis).
<ul style="list-style-type: none"> To evaluate the effect of rilematovir as compared to placebo on medical resource utilization (MRU) with respect to respiratory therapeutic interventions associated with RSV-related disease progression. 	<ul style="list-style-type: none"> Proportion of participants with new antibiotic use, or new or increased use in bronchodilator/nebulizer, systemic corticosteroids, or home oxygen supplementation.
<ul style="list-style-type: none"> To evaluate the effect of rilematovir as compared to placebo on MRU with respect to medically attended visits associated with RSV-related disease progression. 	<ul style="list-style-type: none"> Proportion of participants with unscheduled outpatient clinic visits, emergency room visits or hospitalization for respiratory infection.
<ul style="list-style-type: none"> To evaluate the effect of rilematovir as compared to placebo on the overall RSV-related disease progression. 	<ul style="list-style-type: none"> Proportion of participants meeting a composite endpoint of either developing RSV-related complications (pulmonary & extra pulmonary) and/or needing RSV-related medical attendance.
<ul style="list-style-type: none"> To evaluate the safety and tolerability of rilematovir. 	<ul style="list-style-type: none"> Safety and tolerability, as assessed by AEs, clinical laboratory testing, electrocardiograms (ECGs), physical examination, and vital signs.
<ul style="list-style-type: none"> To evaluate the effect of rilematovir compared to placebo on the clinical course of RSV infection. 	<ul style="list-style-type: none"> Change from baseline over time in severity of the RSV LRTD symptoms as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue) as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of the overall RSV symptoms (URTD [sore throat and nasal congestion], LRTD, and 2 systemic symptoms [feeling feverish and fatigue]) as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of all RSV symptoms as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of each separate RSV LRTD symptom as assessed by the participant using the RiiQ™ Symptom Scale. Time to resolution of respiratory infection symptoms as assessed by the participant using

Objectives	Endpoints
	<p>the Patient Global Impression of RSV Severity (PGI-S) Scale.</p> <p>Definition of resolution in participants without pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> – <i>All LRTD symptoms in the RiiQ Symptom Scale^a scored as ‘None’ (score = 0) or ‘Mild’ (score =1) for at least 24 hours.</i> <p>Definition of resolution in participants with pre-existing respiratory symptoms:</p> <ul style="list-style-type: none"> – <i>Pre-existing symptoms that were worse at baseline should have improved at least 1 point on the RiiQ Symptom Scale from baseline for at least 24 hours; and</i> – <i>Pre-existing symptoms that were not worse at baseline should have not worsened from baseline severity for at least 24 hours, and,</i> – <i>Symptoms that were not pre-existing at baseline should be scored as ‘None’ (score = 0) or ‘Mild’ (score =1) on the RiiQ Symptom Scale for at least 24 hours.</i> <ul style="list-style-type: none"> • Time to return to pre-existing health (status) for all RSV symptoms as assessed by the participant using the RiiQ™ Symptom Scale. • Time to improvement in RSV disease as assessed by the participant using the Patient Global Impression of Change (PGI-C) Scale.
<ul style="list-style-type: none"> • To evaluate the effect of rilematovir compared to placebo on Health-Related Quality of Life (HRQOL). 	<ul style="list-style-type: none"> • Change from baseline over time for the HRQOL as assessed by participants using the EQ-5D-5L and RiiQ™ Impact Scales. • Time to return to usual health as assessed by the participant using the ‘Adult RSV Return to Usual Health’ question. • Time to return to usual activities as assessed by the participant using the ‘Adult RSV Return to Usual Activities’ question. • Time to no or mild impact of RSV-related disease on daily activities, emotions, and social

^a The RiiQ Symptom scale is a four item scale (0: no symptoms, 1: mild symptoms, 2: moderate symptoms, 3: severe symptoms).

Objectives	Endpoints
	relationships as assessed by the participant using the RiiQ™ Impact Scales.
<ul style="list-style-type: none"> To evaluate the antiviral effect of rilematovir as measured by RSV viral load in bilateral nasal mid-turbinate swab samples by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay. 	<ul style="list-style-type: none"> RSV viral load area under the curve from immediately prior to first dose of study intervention (baseline) through Day 3, Day 5, Day 8. Change from baseline over time in RSV viral load. Proportion of participants with undetectable RSV viral load at each time point that a swab is planned to be collected.
<ul style="list-style-type: none"> To evaluate the emergence of mutations in the viral genome potentially associated with resistance to rilematovir. 	<ul style="list-style-type: none"> Post-baseline sequence changes in the RSV F gene.
<ul style="list-style-type: none"> To evaluate the pharmacokinetics (PK) of rilematovir. 	<ul style="list-style-type: none"> Pharmacokinetic parameters of rilematovir (ie, C_{trough}, C_{max}, and AUC_{0-12h}).
<ul style="list-style-type: none"> To evaluate the impact of rilematovir compared to placebo on MRU. 	<ul style="list-style-type: none"> Number and type of medical encounters. Shift in any care setting (e.g. from no assistance to use of skilled home nurse or assisted home living). Proportion of participants requiring hospitalization for respiratory or other reasons and duration of hospitalization (total days length of stay, including incidence and where feasible duration by wards, eg, intensive care unit [ICU]). Incidence and duration of treatment-emergent use of antibiotics. Incidence and duration of treatment-emergent new use or increased dose of systemic or inhaled corticosteroids and bronchodilators. Proportion of participants with new or increased use of oxygen therapy. Duration of oxygen supplementation. Duration of selected post-baseline emergent (after start of study intervention) MRU.
Exploratory	
<ul style="list-style-type: none"> To explore the relationship between antiviral activity and the primary and key secondary clinical outcomes. 	<ul style="list-style-type: none"> Respiratory syncytial virus viral load-based endpoints and primary and key secondary clinical course endpoints.

Objectives	Endpoints
<ul style="list-style-type: none"> To explore the impact of rilematovir compared to placebo on RSV disease-related progression and complications. 	<ul style="list-style-type: none"> The proportion of participants progressing to ICU including the need for mechanical ventilation (yes or no). All-cause mortality up to Day 35.
<ul style="list-style-type: none"> To evaluate the impact of rilematovir compared to placebo on the clinical course of disease using the Clinician Symptom Score (CSS). 	<ul style="list-style-type: none"> Change from baseline over time in the CSS as assessed by a Clinician Questionnaire.
<ul style="list-style-type: none"> To explore the relationship between PK of rilematovir and pharmacodynamics (PD) (selected antiviral activity, clinical outcomes, and safety parameters). 	<ul style="list-style-type: none"> Pharmacokinetic/PD analysis of plasma concentration-time data of rilematovir and selected clinical outcomes, antiviral activity, and safety parameters.
<ul style="list-style-type: none"> To explore the impact of rilematovir compared to placebo on hours missed from work (by all members of the participant's household, including the participant, if employed). 	<ul style="list-style-type: none"> Hours missed from work due to the participant's RSV infection by all members of the participant's household, including the participant, if employed.

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that rilematovir reduces the time to resolution of the RSV LRTD symptoms compared to placebo, as assessed by a PRO measure (RiiQ™) in adult outpatients with at least moderate RSV disease and who are at high risk for RSV disease-related progression.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy, safety, and tolerability of rilematovir at a dose of 250 mg twice daily administered for 7 days in outpatient adults (≥ 18 to ≤ 85 years of age) who are at high risk of RSV-related disease progression, and who have at least moderate RSV disease (LRTD) due to RSV infection. Moderate RSV disease is defined as having at least any 2 of the symptoms of LRTD (*cough, wheeze, coughing up phlegm, short of breath*), one of which must be scored as at least 'moderate' if the symptoms did not pre-exist before RSV onset, OR one of which must be scored worse than usual if the symptoms pre-existed as determined by the participant's ratings of the RiiQ Symptom Scale and the Pre-Existing Symptom Questionnaire in the ePRO device.

A target of 180 participants who are at high risk for RSV-related disease progression will be randomly assigned in a 2:1 ratio (active:placebo) in this study with approximately 120 participants planned in the rilematovir group and approximately 60 participants in the placebo group. Randomization to study intervention treatment should occur within 72 hours after onset of any of the RSV symptoms or worsening of pre-existing symptoms.

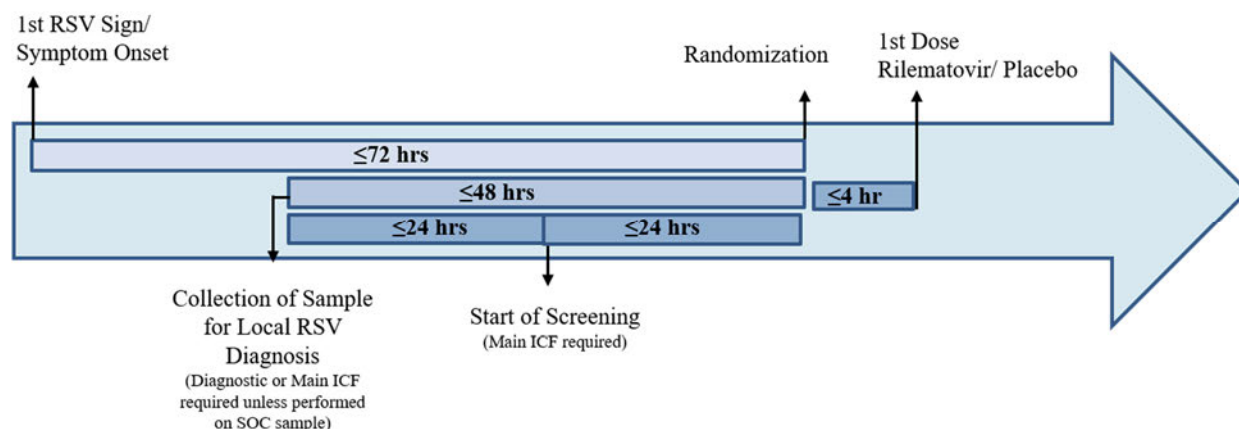
High-risk condition(s) for RSV-related disease progression is defined as:

- Presence of any of the underlying high-risk comorbid cardiopulmonary conditions (COPD, asthma, or CHF) AND/OR
- ≥ 65 years of age (elderly participants)

Randomization will be stratified by high-risk (<65 years of age with underlying high-risk comorbid cardiopulmonary conditions ([COPD, asthma, or CHF] versus ≥ 65 years of age without underlying comorbid cardiopulmonary conditions versus ≥ 65 years of age with underlying comorbid cardiopulmonary conditions), and time since symptom onset (≤ 48 hours versus >48 -72 hours).

The study population should consist of at least 50% of participants with randomization ≤ 48 hours since onset of RSV symptoms. Efforts will be made to include all races and gender.

Figure 2: Timeline from RSV Sign/Symptom Onset to First Dose



ICF = informed consent form; RSV = respiratory syncytial virus; SOC = standard-of-care.

Participants who meet all eligibility criteria will be randomized in a 2:1 ratio to receive 1 of the following 2 treatments:

- Treatment A: rilematovir 250 mg twice daily for 7 days (n = 120)
- Treatment B: placebo twice daily for 7 days (n = 60)

The study will include a screening period (Day -1 to Day 1), a Treatment Period (Day 1 to Day 7/8 [depending on timing of first dose]), and a Follow-up Period (Day 8/9 to Day 35 ± 3). In general, the total study duration for each participant will be 35 (± 3) days. The study is considered complete with the completion of the last study assessment for the last participant in the study.

Study participants will be identified when they present for medical care with symptoms suggesting a diagnosis of RSV infection (eg, nasal congestion, sore throat, dry cough, wheezing, coughing up phlegm [sputum], short of breath, fever and fatigue [tiredness]). Participants must have at least 2 LRTD symptoms, at least one of which is considered of moderate severity as evaluated by the RiiQ Symptom Scale at screening or worsened if the LRTD symptoms were pre-existing based on

the Pre-RSV symptom questionnaire. Screening should be completed as soon as possible. During screening, a bilateral nasal mid-turbinate swab will be collected for local diagnosis of RSV infection preferably using a PCR-based or other molecular-based diagnostic assay. For any patient that is subsequently randomized, the leftover from this sample will be used for central testing of RSV viral load and viral sequencing. However, collection of a study-specific bilateral nasal mid-turbinate (MT) swab at screening is not required if a SOC diagnostic sample is collected within 24 hours of screening start and yields a positive RSV result using a molecular-based diagnostic assay.

Study interventions will be administered orally. Study intervention administration should start as soon as possible, but no later than 4 hours after randomization. Randomization must occur within a window of 72 hours of RSV symptom onset ([Figure 2](#)). The first dose of study intervention will be administered before the participant leaves the site. On Day 1, study-site personnel will provide to the participant all the required study intervention for dosing at home. Study site personnel will instruct participants on how to use and store study intervention for at home dosing.

All participants will complete assessments from Day 1 till the Day 35 visit as stipulated in the [Schedule of Activities](#). Participants will be required to have a study visit at the study site on Day 3, Day 8 (+1), Day 14 (± 1), and Day 21 (± 3). If feasible and allowed per local regulations, a home visit by the home nursing/ study site personnel can be scheduled in situations where the participant is not able to attend on-site due to medical condition or other care situation.

On Day 28 (± 3) and Day 35 (± 3), all participants will be contacted by the study site personnel for a telephone follow-up visit (or other digital call, if possible) to assess the clinical status and medical resource utilization (MRU) and to check for any AEs including RSV-related complications. Participants might be requested, at the discretion of the investigator, to have a safety follow-up visit at the site on Day 28 (± 3) and Day 35 (± 3) in case participants had ongoing AEs or other ongoing laboratory, vital signs or ECG-related abnormalities at the previous visit.

Patient-reported outcomes will be done throughout the study as stipulated in the [Schedule of Activities](#) (see Section [8.1](#)).

Evaluation of clinical assessment of the RSV clinical course will be explored using a Clinician Symptom Score (CSS) based on the Clinician Questionnaire at timepoints as stipulated in the [Schedule of Activities](#). This is a respiratory symptom score based on clinician interview of the participant to evaluate RSV LRTD symptom severity and to determine the degree of improvement following study intervention.

One of the secondary efficacy endpoints is the incidence of treatment-emergent complications associated with RSV. RSV-related complications (pulmonary and extra pulmonary) will be identified by the treating investigator based on protocol guided definition of complications and the required clinical data.

Medical resource utilization will be assessed (see Section [8.7](#)).

Safety and tolerability, including AEs, laboratory assessments, ECGs, physical examination, and vital signs will be assessed throughout the study from signing of the main informed consent form (ICF) until the participant's last study-related activity (see Section 8.2). For participants having signed only a diagnostic ICF, only procedure-related AEs will be reported.

A bilateral nasal mid-turbinate swab will be taken on Day 1 (predose) for the central laboratory confirmation of RSV infection, determination of RSV viral load (and RSV subtype), determination of the presence of other respiratory viruses or bacteria and viral sequencing. This sample is not to be collected if a study-specific screening bilateral nasal mid-turbinate swab was taken within 8 hours before the first dosing, in which case the leftover of that sample can serve as the baseline predose sample, provided that the sample was stored appropriately and sufficient sample volume is available (volume is considered sufficient if no more than 600 µL from the original sample has been used for local RSV testing and the entire remainder of the original sample is available). However, when a local RSV diagnosis was performed using a SOC sample, then this Day 1 predose sample is required to be collected in any case. In addition, bilateral nasal mid-turbinate swabs for RSV viral load quantification and viral sequencing will be collected throughout the study (Section 8.1.3).

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a popPK model (Section 8.4).

Blood samples collected for biomarker research (eg, RNA, proteins including cytokines, cellular phenotyping) may be analyzed at the sponsor's discretion on the premise that these markers may play a role in the treatment response, safety or PK of rilematovir, or RSV-related disease. Leftover nasal mid-turbinate swabs and blood samples collected for other testing may be used as well for the same purpose (see Section 8.5).

The presence of other respiratory viruses or bacteria in nasal swabs will be assessed (see Section 8.6).

A separate Substudy to explore the use of Biosensors for monitoring cardio-respiratory parameters will be performed at selected study sites in a subset of participants who provide specific consent for this assessment. Details, including objectives and study design, will be described in a separate Substudy protocol.

A second Substudy with Qualitative Patient Interviews will be performed at selected study sites in a subset of participants who provide specific consent for this assessment. This Substudy will gain insight in the participants experience throughout the clinical course of their RSV infection, and to guide interpretation of treatment outcomes and study endpoints. Details, including objectives and study design, will be described in a separate Substudy protocol.

Interim analyses may be conducted at the sponsor's discretion when at least approximately 65% of participants are enrolled to review futility as well as clinical outcome trends to allow (or initiate) preparation towards a Phase 3 study design. The interim analysis will preferably be conducted at the end of a northern or southern hemisphere RSV season (Section 9.5).

An IDMC will be commissioned for this study to monitor safety data on a regular basis (see Section 9.6)

Participants who prematurely discontinue study intervention for any reason (except withdrawal of consent) are recommended to remain compliant to all study-related procedures including timely completion of all the efficacy assessments (e.g., RiiQ/other PRO questionnaires) up to Day 35. Participants who withdraw consent to participate in the study during the treatment or follow-up phase will be offered an optional Safety Follow-up visit which will consist of the same assessments as at the Final Study Visit (Day 35).

When participants are hospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the Schedule of Activities, if practically feasible.

See Appendix 10.20 for guidance on study conduct during the Coronavirus Disease 2019 (COVID-19) pandemic.

A diagram of the study design is provided in Section 1.2.

4.2. Scientific Rationale for Study Design

Study Population

The study population targets immunocompetent adult participants ≥ 18 to ≤ 85 years of age diagnosed with RSV infection in an outpatient setting who are at high risk for RSV-related disease progression.

While RSV typically presents in adults as self-limited URTD or LRTD, it is a significant cause of severe respiratory infection in elderly adults aged ≥ 65 years of age (Duncan 2009, Falsey 2005, Jain 2015) and in adults (regardless of age) with underlying cardiopulmonary comorbidities such as asthma, COPD, and CHF (Duncan 2009, Falsey 2005, Falsey 2019). Among elderly adults who are at risk for severe RSV disease, RSV infection may manifest as severe, life-threatening LRTD with pneumonia, requirement for ventilatory support, and short- and long-term morbidity (Tseng 2020). In the US, an annual estimated 61,000-177,000 hospitalizations and 10,000-14,000 deaths are attributable to RSV in adults ≥ 65 years of age (Falsey 2005). In a longitudinal assessment over 12 RSV seasons in a single outpatient community (n=13,809), the relative risk of a serious outcome (ie, hospitalization, emergency room visit, and pneumonia) was significantly increased in RSV-infected persons aged ≥ 75 years of age (versus 60-64 years of age) and in those with COPD or CHF (Belongia 2018).

Current treatment options for RSV are generally supportive in nature, consisting of supplemental oxygen, intravenous fluids, and bronchodilators. No vaccines or antivirals have been approved for the prevention or treatment of RSV infection in adults. Aerosolized, oral, and intravenous ribavirin have been used selectively in RSV-infected immunocompromised adults with variable results (Nam and Ison 2019). Due to the significant disease burden and the lack of effective treatment, the

unmet medical need (prophylactically and therapeutically) is substantial, especially related to antiviral treatment in the high-risk adult population as described above.

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical and virologic endpoints that may occur in the absence of active intervention. The use of a placebo control will allow for any AEs or laboratory abnormalities observed during the course of the study to be evaluated properly, ie, to differentiate between events potentially related to the use of rilematovir versus those related to the underlying disease. In addition, no approved treatments are available to allow comparison.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Eligible participants will be randomized in a 2:1 ratio to receive either Treatment A (rilematovir 250 mg twice daily) or B (matching placebo twice daily).

Stratification Factors

Randomization will be stratified by high-risk (<65 years of age with underlying high-risk comorbid cardiopulmonary conditions [COPD, asthma, or CHF] versus ≥ 65 years of age without underlying comorbid cardiopulmonary conditions versus ≥ 65 years of age with underlying comorbid cardiopulmonary conditions), and time since symptom onset (≤ 48 hours versus > 48 -72 hours). The study population should consist of at least 50% of participants with randomization ≤ 48 hours since onset of RSV symptoms.

Study and Dosing Duration

A twice daily dosing regimen for 7 days (14 consecutive doses) is employed as data have shown that the duration of viral shedding after RSV infection is at least that long. Seven days was also the duration of dosing in the healthy volunteer challenge study in adults (study 53718678RSV2001), in the completed study 53718678RSV1005 in pediatric participants, the pilot Phase 2a study in adults (Study 53718678RSV2004), and in the ongoing Study 53718678RSV2002 in RSV-infected pediatric participants, in which rilematovir was generally safe and well tolerated (see Section 2.2).

Interim Analysis

Refer to Section 9.5.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue

participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is the use of placebo in this population. The rationale for using placebo is outlined in Section 4.2.

The total blood volume (maximum approximately 80 mL) to be collected is considered to be acceptable over this time period from the population in this study.

4.3. Justification for Dose

Participants will be administered 250 mg rilematovir twice daily for 7 days. Co-administration of moderate or strong CYP3A4 inhibitors will require dose reduction of rilematovir to 125 mg twice daily for 7 days. Co-administration with certain strong CYP3A4 inhibitors such as posaconazole or ketoconazole is however not allowed in this study. Please refer to Section 2.2 for details on the interaction with CYP3A4 inhibitors and Section 6.8 for details on CYP3A4 inhibitors that are allowed but require dose adjustment.

In the Phase 2a Study 53718678RSV2004, 2 dose levels of 500 mg and 80 mg once daily were investigated compared to placebo. The choice of the dosing regimens in that study was based on the results of the human challenge Study 53718678RSV2001, in which target engagement for rilematovir was demonstrated in immunocompetent adults inoculated with RSV-A Memphis 37b. In Study 53718678RSV2001, exposure to rilematovir resulted in a reduction of viral load over time in all 3 rilematovir dose groups (75, 200, and 500 mg once daily) as compared to the placebo group, without an apparent exposure-antiviral effect relationship. The protein-adjusted 90% effective concentration ($paEC_{90}$) of rilematovir against the RSV-A rgRSV224 strain was calculated as 41 ng/mL. The doses of 75, 200, and 500 mg once daily had mean C_{trough} levels of 50, 85, and 334 ng/mL, respectively, and were all above the $paEC_{90}$. Since all dose regimens were generally safe and well tolerated, the highest dose of 500 mg once daily was selected for subsequent adult studies to minimize the risk of development of drug resistance and to ensure the highest potential for antiviral effect. Doses of 500 mg once daily provide trough levels of at least 8- to 13-fold greater (~300 to 550 ng/mL, as observed in Studies 53718678RSV1001 and 53718678RSV2001) than $paEC_{90}$ levels.

Adult Study 53718678RSV2004 confirmed the appropriateness of the 500 mg once daily dose in terms of trends of favorable antiviral and clinical effects. The results in adult participants infected with RSV demonstrated better clinical outcome with the 500 mg rilematovir once daily dose compared to the 80 mg rilematovir once daily dose.

However, due to exposure (C_{max})-related important potential risk of QT interval prolongation identified from the analysis of the TQT Study 53718678RSV1009 (see Section 2.2), the sponsor has performed additional modeling to evaluate alternative dose and dosing regimens, which would allow to maintain the plasma concentration (C_{trough}) at effective levels and maintain AUC exposure while reducing the C_{max} , to mitigate this potential risk. The updated popPK model is suitable for

PK simulations to adequately predict C_{\max} , AUC, and C_{trough} after single and multiple doses of rilematovir.

The physiologically-based pharmacokinetic (PBPK) model developed to assess the potential drug-drug interactions with rilematovir as victim was updated in SimCYP V19 to investigate the effect of concomitant administration of strong and moderate CYP3A4 inhibitors on the single dose and steady state C_{\max} and AUC of rilematovir following dosing (Table 1). Based on the analyses, the use of moderate or strong CYP3A4 inhibitors has a similar effect on steady-state C_{\max} (1.5-fold), albeit a different effect on steady-state AUC_{0-24h} (up to 2-fold for moderate CYP3A4 inhibitors and up to 3-fold for strong CYP3A4 inhibitors).

Table 1: Simulated Effect of Concomitant CYP3A4 Inhibitors on Rilematovir PK Parameters

PK Parameter	Strong CYP3A4 Inhibitors ^a	Moderate CYP3A4 Inhibitors ^b
C_{\max} single dose	1.5-fold	1.5-fold
AUC _{0-24h} single dose	3-fold	2-fold
C_{\max} multiple doses	1.5-fold	1.5-fold
AUC _{0-24h} multiple doses	2.5-fold	2-fold

PK: pharmacokinetic, CYP: cytochrome P450, AUC_{0-24h} = area under the plasma concentration-time curve from time of administration up to 24 hours postdose, C_{\max} : maximum plasma concentration.

Note: The effect of strong inhibitors on AUC single dose and AUC multiple doses was also evaluated as 3.5-fold. (Based on single-dose PK results of Study 53718678RSV1006. In this scenario, the effect of CYP3A4 induction on comedication is excluded).

^a Based on itraconazole simulations.

^b Based on eg diltiazem simulations.

The PBPK model was used to simulate the PK parameters for rilematovir following a multiple 125 mg twice daily dose in the presence of strong CYP3A4 inhibitors (200 mg twice daily voriconazole, 500 mg twice daily clarithromycin, or 400 mg twice daily posaconazole) in healthy participants. Concomitant administration of voriconazole, clarithromycin, and posaconazole resulted in a 2.80, 2.88, and 4.73-fold increase, respectively, in steady state AUC_{0-24h} values and a 1.77, 1.82, and 2.48-fold increase, respectively, in $C_{\max,ss}$ of rilematovir.

Simulations were conducted using the popPK model, the effect of comedication and the $\Delta\Delta Q_{TcI}$ in the model (taking into account variance-covariance matrix of the drug-effect slope, plasma effect site equilibration rate constant [Ke_0] and intercept) with 1,000 virtual adult participants re-sampled from the 53718678RSV2004 data. The summary statistics of the simulation are presented in Table 2.

Table 2: Predicted Geometric Mean AUC_{0-24h}, C_{max}, C_{trough} and ΔΔQTcI After Day 1 and Day 7

PK Parameters	250 mg bid	125 mg bid + moderate CYP3A4 inhibitors ^a	125 mg bid + strong CYP3A4 inhibitors ^b
AUC _{0-24h} Day 1 (ng hr/mL)	24,700	23,300	35,000/40,800 ^b
AUC _{0-24h} Day 7 (ng hr/mL)	40,700	35,800	44,800/62,700 ^b
C _{max} Day 1 (ng/mL)	1,950	1,430	1,430
C _{max} Day 7 (ng/mL)	2,560	1,780	1,780
C _{trough} Day 1 (ng/mL)	710	623	935
C _{trough} Day 7 (ng/mL)	1,070	881	1,100
ΔΔQTcI Day 1 (ms) (90%CI)	2.98 (1.69-5.06)	2.66 (1.49-4.53)	2.66 (1.49-4.53)
ΔΔQTcI Day 7 (ms) (90%CI)	4.12 (2.10-7.66)	2.95 (1.48-5.61)	2.95 (1.48-5.61)

ΔΔQTcI: placebo-corrected change from baseline for the individual-corrected QTc, AUC_{0-24h}: AUC from time of administration up to 24 hours post dosing, bid: twice daily, C_{trough}: predose plasma concentration, CI: confidence interval, C_{max}: maximum plasma concentration, CYP: cytochrome P450, PK: pharmacokinetic(s), PBPK: physiologically-based pharmacokinetic(s).

a. Based on PBPK modeling.

b. Based on single dose PK results of 53718678RSV1006.

In study 53718678RSV1001, the 250 mg twice daily regimen provided C_{trough} levels that are somewhat higher than those observed with the 500 mg once daily regimen (mean [SD] C_{trough} levels on Day 7 of 550 [477] ng/mL and 643 [126] ng/mL [n=6] for 500 mg once daily and 250 mg twice daily, respectively). The dose regimen of 250 mg twice daily provides similar exposure levels (AUC_{0-24h}), higher C_{trough} levels and lower C_{max} levels compared to the 500 mg once daily regimen, which should translate to at least similar efficacy of rilematovir as well as maintain the favorable safety profile.

Based on final PK, QTc, and PBPK modeling (for interaction with moderate and strong CYP3A4 inhibitors), a 7-day dosing regimen of 250 mg twice daily is selected for the adult Phase 2b study. The dose is to be reduced to 125 mg twice daily when patients are co-administered or may require initiation of moderate to strong CYP3A4 inhibitors, including macrolide antibiotics and antifungals, which are important in the population with high risk of RSV-related disease progression and complications. Co-administration with posaconazole or ketoconazole is not allowed in this study. The upper limit of the 90% CI for ΔΔQTcI for the twice daily regimen in combination with moderate or strong CYP3A4 inhibitors remains below 10 ms for each of the groups (Table 2).

Overall, based on all currently available data, it is anticipated that the selected twice daily dosing of rilematovir will be in the therapeutic range for adults, ensuring the highest potential antiviral effect while minimizing the risk of development of resistance (by increasing C_{trough} [mean C_{trough} will exceed more than 10 times the paEC₉₀ of 41 ng/mL]), as well as mitigating the potential risk of QT interval prolongation (by decreasing C_{max}).

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last phone visit or on-site visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion

of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed dosing and has completed assessments at Day 35 (± 3 days) of the double-blind phase.

5. STUDY POPULATION

Screening for eligible participants will be performed as soon as possible after presentation to the healthcare facility, such that participants are randomized within 72 hours of RSV symptom onset. Treatment is initiated as soon as possible, but no later than 4 hours after randomization.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

Each potential participant must satisfy all the following criteria to be enrolled in the study:

Age

1. 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 85 years of age, inclusive.

Type of Participant and Disease Characteristic

2. Presentation to the healthcare facility with symptoms suggestive of a diagnosis of acute RSV infection and have at least any 2 of the following symptoms of LRTD, one of which must be scored as at least 'moderate' if the symptoms did not pre-exist before RSV onset, OR one of which is scored worse than usual if the symptoms pre-existed as determined by the participant's ratings of the RiiQ Symptom Scale and the Pre-Existing Symptom Questionnaire in the ePRO device.

LRTD symptoms: *cough, wheezing, short of breath, coughing up phlegm (sputum).*

3. Tested positive for RSV infection using a molecular-based diagnostic assay (PCR or other) on a bilateral nasal mid-turbinate swab sample as part of the study-specific screening assessment or on a respiratory tract sample as part of SOC testing (collected within 24 hour prior to start of screening).

4. Participants must have at least one of the following high-risk conditions that predispose them to RSV-related disease progression:
 - a. Age ≥ 65 years
 - b. CHF
 - c. COPD
 - d. Asthma.
5. Randomized to study intervention treatment within 72 hours after onset of any of the RSV symptoms or worsening of pre-existing symptoms.

Onset of symptoms is defined as the time the participant becomes aware of the first sign and/or symptom or worsening of sign and/or symptom consistent with a viral infection. Efforts should be made to determine the time of onset of symptoms as accurately as possible (in relation to routine daily activities).

Note: The study intervention administration should start as soon as possible, but no later than 4 hours after randomization.
6. Not be hospitalized during screening. Emergency room or hospital observation status for an anticipated duration of <24 hours are not considered as hospitalization.
7. Except for the RSV-related disease, the participant must be medically stable based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening. Any abnormalities must be consistent with the underlying illness (RSV disease and/or comorbid condition) in the study population as evaluated by the investigator. This determination must be recorded in the participant's source documents and initialed by the investigator.
8. The participant must have been assessed per local public health practice and considered not to have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during this respiratory infection.

Sex and Contraceptive/Barrier Requirements

9. A woman must be (as defined in Appendix 10.5)
 - a. Not of childbearing potential
 - b. Of childbearing potential and
 - Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and

correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are in Appendix 10.5.

- Have a negative urine pregnancy test (β -human chorionic gonadotropin [β -hCG]) at screening.

10. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 30 days after the last dose of study intervention.
11. From Day 1 during the study and for 90 days after receiving the last dose of study intervention, a male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

Note: Contraceptive (birth control) use by participants should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

12. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last dose of study intervention.

Informed Consent

13. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

Note: Prior to signing the main ICF for the study, participants may specifically allow for the collection and testing of study-specific bilateral nasal mid-turbinate swabs by signing the pre-screening (diagnostic) ICF. This is not applicable if a positive RSV diagnostic result, based on a local SOC sample collected within 24 hours prior to start of screening, is available and used for determining study eligibility.

14. Willing and able to adhere to the lifestyle restrictions specified in this protocol (see Section 5.3).

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

1. History of or concurrent disease (with the exception of COPD, asthma, CHF), or clinically significant findings during screening or medical history, physical examination, laboratory testing, vital signs, ECG recording, for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being).
2. Any condition that could prevent, limit, or confound the protocol-specified assessments (eg. participant is unable to understand and answer questions in one of the official language versions provided for the PRO assessments to participate in the study or is illiterate).
3. Known allergies, hypersensitivity, or intolerance to rilematovir or to any of the excipients of rilematovir or placebo formulation (refer to the IB; [IB 2020](#)).
4. Presence of clinically significant heart arrhythmias, uncontrolled, unstable atrial arrhythmia, or sustained ventricular arrhythmia.
5. Unstable angina pectoris or myocardial infarction within 30 days prior to screening (inclusive).
6. Recent history (<2 months before screening) of clinically relevant electrolyte disorders related to hypokalemia and/or hypomagnesemia, as per investigator assessment, that have not been adequately managed.
7. Confirmed corrected QT (QTcF) interval >450 ms per the machine read ECG parameter result at screening. Presence of an abnormal QTcF interval should be confirmed by repeat ECG recording during screening.
8. Presence of repetitive ventricular premature contractions (>10/min), second (Type II or Mobitz Type II) or third-degree heart block, or incomplete or complete left bundle branch block, or complete right bundle branch block per the machine read ECG results at screening. Presence of any of the above abnormalities should be confirmed by repeat ECG recording during screening.
9. Other clinically significant abnormal ECG findings not consistent with the underlying condition in the study population, as judged by the investigator based on the machine read ECG results at screening.
10. Participants who are considered by the investigator to be immunocompromised within the past 12 months, whether due to underlying medical condition (eg, malignancy or

genetic disorder other than immunoglobulin A deficiency, or human immunodeficiency virus [HIV] infection, eg, CD4+ count <200 cells/mm³) or medical therapy (eg, medications other than corticosteroids for the treatment of COPD or asthma exacerbations, chemotherapy, radiation, stem cell or solid organ transplant).

11. Participant has known or suspected (from medical history or participant examination) chronic or acute hepatitis B or C infection.
12. The participant has had either:
 - a) Confirmed SARS-CoV-2 infection (test positive) during the four weeks prior to randomization,
 - OR
 - b) Close contact with a person with COVID-19 (test confirmed or suspected SARS-CoV-2 infection) within 14 days prior to randomization.
13. Participants unable to take medications orally or with a known gastrointestinal-related condition that is considered by the sponsor or investigator to be likely to interfere with study intervention ingestion or absorption.
14. Participants unwilling to undergo bilateral nasal mid-turbinate swab procedures or with any physical abnormality which limits the ability to collect regular nasal specimens.
15. Participant had major surgery (eg, requiring general anesthesia) within 28 days before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

16. Living in institutional care or assisted living facility and also receiving acute care management for any respiratory condition.

Note: Institutional care refers to a place of residence that provides nursing supervised assistance with activities of daily living, healthcare, and rehabilitation.

Prior/Concomitant Therapy

17. Taken any disallowed therapies as noted in Section 6.8 before the planned first dose of study intervention.

Prior/Concurrent Clinical Study Experience

18. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study intervention or is currently enrolled in an investigational study.

Note: COVID-19 vaccines with Emergency authorized approvals are not considered investigational.

19. Participant with current or planned participation in another clinical study where study intervention/investigational device is being administered while participating in the current study.

Other Exclusions

20. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
21. Women who are pregnant or breastfeeding.
22. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.
23. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 10.3.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Concurrent administration of medications/use of licensed devices is allowed as supportive therapy per local SOC, as long as the medication/licensed device will not affect the participant's participation in the study and is in accordance with allowed concomitant therapy.

COVID-19 vaccine administration during study period: As side effects due to vaccination may impact the evaluation of the clinical evolution of RSV symptoms, it is recommended that administration of a COVID-19 vaccine be timed to occur after study completion or at least two weeks after the last dose of study medication. Investigator discretion and overall assessment of clinical stability will be relied on if there is a medical need to administer vaccine to a participant during the study period. Study intervention as well as the follow up can continue as scheduled.

Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study.

2. Participants may not consume food or beverages containing grapefruit juice during rilematovir dosing period.
3. Agree to be compliant with the completion of the ePROs per the required schedule.
4. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, but not in the same acute respiratory infection episode in case RSV(-) diagnosis was the reason for screen failure.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Eligible participants will be randomized in a 2:1 ratio (active:placebo) to receive either rilematovir or placebo for 7 days twice daily (14 consecutive doses).

Study interventions will be administered orally. Study intervention administration should start as soon as possible, but no later than 4 hours after randomization. Randomization must occur within a window of 72 hours of RSV symptom onset. For analysis purposes, the day of first study intervention administration will be considered Day 1.

Description of Interventions

Arm Name	Treatment A	Treatment B
Intervention Name	Rilematovir (JNJ-53718678)	Placebo
Type	Drug	Drug

Arm Name	Treatment A	Treatment B
Dose Formulation	Oral film-coated tablet	Oral film-coated tablet
Unit Dose Strength(s)	eq. 125-mg	Matching placebo
Dosage Level(s)	250 mg twice daily (bid) for 7 days (dose reduction to 125 mg bid if coadministration with moderate or strong CYP3A4 inhibitors is started or continued during study intervention treatment) ^a	Matching placebo bid for 7 days
Route of Administration	Oral	Oral
Use	Experimental	Placebo
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product	No	No
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	The oral film-coated tablets are packaged in high-density polyethylene (HDPE) bottles with child-resistant screw caps with 2 g of desiccant.	
	Labels will contain information to meet the applicable regulatory requirements.	
Delivery Instructions	Do not crush tablets. All study drugs will be taken orally with a glass of water.	
Food/Fasting Requirement	Regardless of food administration	
Other Requirements	Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM)	
^a Refer to Section 6.8 for details regarding the coadministration of moderate or strong CYP3A4 inhibitors during the study. Investigators must review the concomitant medications at screening and consult the sponsor as needed.		

Rilematovir will be administered as an eq. 125-mg (G033, containing 143.75 mg of JNJ-53718678-ZCL, hemi-tartrate, equivalent to 125 mg JNJ-53718678-AAA, the free form drug substance) or placebo (G037) oral film-coated tablet.

Rilematovir oral film-coated tablets will be manufactured and provided under the responsibility of the sponsor. The rilematovir film-coated tablets contain the following excipients: hypromellose 2910 15 mPa.s, sodium laurilsulfate, lactose monohydrate, croscarmellose sodium, silicified microcrystalline cellulose, silica (colloidal anhydrous), magnesium stearate, coating powder yellow and purified water (removed during processing). The matching placebo film-coated tablets contain the following excipients: lactose monohydrate, croscarmellose sodium, silicified microcrystalline cellulose, silica (colloidal anhydrous), magnesium stearate, coating powder yellow and purified water (removed during processing).

Dosing Instructions

Rilematovir will be dosed as 250 mg twice daily for 7 days. In case coadministration of the class of strong or moderate CYP3A4 inhibitors is started or continued during study intervention treatment, the dose needs to be adjusted to 125 mg twice daily. **Note:** Coadministration with posaconazole or ketoconazole is not allowed in this study (see Section 6.8).

Depending on the time of randomization/enrollment, participants will receive 1 dose (PM) or 2 doses (AM and PM) of study intervention on Day 1. Administration of the second dose may be delayed or brought forward (by maximum of 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. For participants who receive only 1 dose of study intervention on Day 1 (PM), dosing should continue until the morning of Day 8 (AM) so that all participants receive 14 consecutive doses in total.

Dosing should occur approximately every 12 hours at approximately the same time each day. The study intervention can be administered with/without food. In case a dose was missed, the dose should be given as soon as possible but within 6 hours after the scheduled time. If more than 6 hours have elapsed, the dose should be skipped, and the next dose should be taken at the next scheduled time point per the initial dosing schedule. In case of vomiting >6 hours after dosing or in case of no visual confirmation of tablet in the vomit, the participant should not be re-dosed.

The first dose of study intervention will be administered before the participant leaves the site on Day 1. The date and time of study intervention administration must be captured in the source documents and the electronic case report form (eCRF). Study site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

For a definition of study intervention overdose, refer to Section 6.7.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored as specified on the label.

Refer to the pharmacy manual or study site investigational product and procedures manual for additional guidance on study intervention handling and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The first dose of study intervention dispensed to the participant at Day 1 must be documented on the intervention accountability form. For doses administered at home, the dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

At the study site, study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention (Treatments A or B; 2:1 ratio [active: placebo] randomization) groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Randomization will be stratified by high-risk (<65 years of age with underlying high-risk comorbid cardiopulmonary conditions [COPD, asthma, or CHF] versus ≥ 65 years of age without underlying comorbid cardiopulmonary conditions versus ≥ 65 years of age with underlying comorbid cardiopulmonary conditions), and time since symptom onset (≤ 48 hours versus $> 48-72$ hours). The study population should consist of at least 50% of participants with randomization ≤ 48 hours since onset of RSV symptoms. To ensure the enrollment of participants with randomization ≤ 48 hours since onset of RSV symptoms of a minimum of approximately 50% of all participants, a cap (at a maximum of 50%; ie 90 participants) on the enrollment of the participants with randomization $> 48-72$ hours since onset of RSV symptoms will be applied.

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, rilematovir plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the case report form eCRF. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded will be asked to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis.

6.4. Study Intervention Compliance

At the screening/predose visit, study site personnel will instruct participants on how to use and store study intervention for at home dosing. Participants will be provided with study intervention for daily use at home and will be requested to document date and time of intakes.

During the course of the study, the investigator or designated study site personnel will be responsible for ensuring the participants are compliant with taking in the study intervention, and for providing additional instruction to reeducate any participant who is not compliant with taking in the study intervention.

Participants will be asked to return the remainder of the study intervention and/or empty packaging to the site on the Day 8 visit for compliance checking (including count of any study drug returned).

Discrepancies will be discussed with the participant and date and time of study drug intakes recorded in the source documents and the eCRF.

The study intervention will be administered orally.

Missed doses of rilematovir or placebo will be recorded in the source documents and the eCRF.

6.5. Dose Modification

Any dose/dosage adjustment should be overseen by medically qualified study site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

No dose modification is allowed unless coadministration of the class of strong or moderate CYP3A4 inhibitors is started or continued during study intervention treatment, in which case the dose of rilematovir needs to be adjusted to 125 mg twice daily (see Sections 6.1, 4.3, and 6.8).

Note: Coadministration of posaconazole or ketoconazole is not allowed in this study.

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

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine SOC.

6.7. Treatment of Overdose

For this study, any dose of rilematovir greater than the total daily dose within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE, ECG and laboratory abnormalities until rilematovir can no longer be detected systemically (at least 3 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

Concomitant medications and supportive therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of drug/therapy, treatment duration (dates of treatment start and stop), dosing regimen, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study; however, if a participant has received acute doses of a prohibited drug, switching to an alternative drug chosen at the discretion of the investigator will be allowed.

Participants will be required to document the use of concomitant medication in the participants notes from signing of the main ICF until the last study visit, which will serve as source document for the study site personnel to complete the eCRF.

Allowed Medications

Participants can receive medications such as acetaminophen/paracetamol, non-steroidal anti-inflammatory drugs, leukotriene antagonists, or antihistamines, considering their respective package insert, at the investigator's discretion prior to and during the study.

Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted, including:

- Inhaled β -agonists or anticholinergics (also permitted as maintenance therapy for the underlying asthma or COPD);
- Inhaled corticosteroids and, to a certain extent, systemic corticosteroids (see below);
- Oral/intravenous/intramuscular antibiotics such as β -lactams and macrolides.

Note: The temporary use of over-the-counter medications in the 14 days prior to randomization and during the study is permitted. The use of vitamins and mineral supplements is also permitted.

Prescription medications, known to be moderate or strong inhibitors of CYP3A4 enzymes that are allowed but require rilematovir dose adjustment as described in Section 6.1, are listed in Table 3.

As side effects due to seasonal (eg. flu) or other routine (eg. pneumococcal) vaccinations may impact the clinical evolution of RSV symptoms, it is recommended that administration of these vaccines be timed to occur after study completion or at least two weeks after the last dose of study medication. Investigator discretion and overall assessment of clinical stability will be relied on if there is a medical need to administer vaccine to a participant during the study period. Study intervention as well as the follow up can continue as scheduled.

Disallowed Medications

The following medications are not permitted during the study and for the time period prior to screening as noted:

- Herbal supplements with active metabolic enzyme inducing components (eg, St-John's Wort) within 21 days or breast cancer resistance protein (BCRP, a transporter protein) inhibiting components (eg, curcumin) within 2 days prior to randomization. This does not apply to herbal teas, herbal supplements without confirmed strong CYP3A4 inhibitory/inductive activity, and/or homeopathy.
- Any investigational vaccine, including investigational RSV vaccines, at any time prior to and during the study.

Note: COVID-19 vaccines with Emergency authorized approvals are not considered investigational.

- Systemic corticosteroids if used for >7 consecutive days immediately prior to screening at doses higher than 20 mg/day of prednisone or equivalent (unless indicated to treat underlying COPD/asthma). Participants meeting the eligibility criteria at screening but requiring initiation or increased doses of systemic corticosteroids (>20 mg/day of prednisone or equivalent) for a prolonged period (>7 consecutive days) during the study due to the underlying conditions are allowed to continue participation in the study.
- Prescription medications with a known risk to prolong the QT interval can be continued if the participant is already on a stable therapy prior to screening and if the QTc interval meets the eligibility criteria, however, the use of these medications cannot be initiated at screening and/or during the study intervention treatment period (see [Table 3](#) and [Appendix 10.8](#)).
- The following prescription medications within 14 days prior to screening and during the study:
 - Prescription medications intended to prevent or treat the RSV infection itself (eg, inhaled/oral ribavirin, intravenous RSV immunoglobulin). Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted.
 - Prescription medications which are known to be a moderate or strong inhibitor of CYP3A4 enzymes, with the exception of posaconazole and ketoconazole, are only permitted during the study period if accompanied by a dose reduction of rilematovir (125 mg twice daily dose) as listed in [Table 3](#).
 - Prescription medications which are known to be a strong inducer of CYP3A4 enzymes as listed in [Table 3](#).
 - Prescription medications that are known to be BCRP inhibitors including eltrombopag, fostamatinib, rolapitant, and teriflunomide within 5 times their respective half-lives prior to randomization.
- Palivizumab, within 5 half-lives (approximately 100 days) prior to screening.
- Any other investigational drug within 30 days or 5 elimination half-lives of that drug (whichever is longer) prior to screening and during the study.
- Prior exposure to rilematovir at the time of screening.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Table 3: Examples of Commonly Used Medications With CYP3A4 Inhibiting and/or QT Prolonging Effects Which are Disallowed or Allowed Upon Coadministration with Rilematovir

Drug Class	CYP3A4 Inhibitors Allowed with Dose Reduction ^a	QT Prolonging Drugs Allowed with Restrictions ^b	CYP3A4 Inhibitors + QT Prolonging Drugs Allowed with Dose Reduction and Restrictions ^c	CYP3A4 Inhibitors/Inducers +/- QT Prolonging Effects Disallowed ^d
Antifungals	itraconazole, isavuconazole, ravuconazole	Pentamidine	fluconazole, voriconazole	posaconazole, ketoconazole
Macrolide antibiotics	troleandomycin	Azithromycin	clarithromycin, erythromycin	
Ketolide antibiotics	telithromycin			
Fluoroquinolones		levofloxacin, moxifloxacin	ciprofloxacin	
Antidepressants	nefazodone			
Calcium channel blocker	verapamil			
Immunomodulators	cyclosporine			
Anti-arrhythmics		disopyramide, procainamide, quinidine, sotalol		amiodarone, flecainide, mexiletine, propafenone, systemic lidocaine
Antipsychotics		haloperidol, thioridazine, ziprasidone		
Antidepressants		citalopram, escitalopram		
Antiemetics		dolasetron, droperidol, granisetron, ondansetron		
Antihistamines				astemizole, terfenadine
Gastrointestinal/gastroesophageal reflux disease drugs				cisapride

This list is not exhaustive. Investigators must consult with the sponsor for any additions or updates to this list. For medications with a known risk to prolong the QT interval investigators are referred to the complete list available at <https://www.crediblemeds.org/pdf/temp/pdf/CombinedList.pdf>. Investigators must check regularly for any additions or updates to this list (see Appendix 10.8).

- Dose reduction required in case of coadministration of rilematovir with strong or moderate CYP3A4 inhibitors (see Section 6.1).
- Medications with a known risk to prolong the QT interval can be continued if the participant is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria, however, the use of these medications cannot be initiated at screening and/or during the study intervention treatment period.
- Medications with CYP3A4 inhibitory effects in addition to QT interval prolonging effects are allowed if the participant is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria, but require dose adjustment (see Section 6.1). However, the use of these medications cannot be initiated at screening and/or during the study intervention treatment period.
- Disallowed within 14 days prior to screening and during the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant.
- The participant has a confirmed QTc interval value >500 ms at any scheduled visit, per the machine read parameter result. Confirmation needs to be obtained immediately by another machine read ECG locally at the site.
- The participant is reported with laboratory abnormality of hypokalemia of <2.5 mEq/L and/or hypomagnesemia of <0.9 mEq/L in samples taken at screening or any time during the study intervention treatment period, confirmed in a repeat test done locally, to be performed within 24 hours of the result being available at the site.
- The participant is reported with laboratory abnormality of alanine transaminase (ALT) increase ≥ 3 x upper limit of normal (ULN) in samples taken at any time during the study intervention treatment period and met the liver safety management discontinuation criteria (see Appendix 10.6).
- The participant is reported with any other laboratory abnormality of Grade 3 or 4 (except for Grade 3 or 4 elevations of triglycerides, low density lipoprotein cholesterol, and/or cholesterol), considered as possibly related to study intervention and confirmed in a repeat test done locally, to be performed within 48 hours of the result being available at the site.
- The participant is poorly compliant with completing ePRO questionnaires, preferably after evaluation and discussion between the investigator and the sponsor.
- The randomization code is broken by the investigator or the study-site personnel.
- Lost to follow-up.
- Sponsor's decision to terminate the study.

If a participant prematurely discontinues study intervention treatment for any reason, he or she is recommended to remain compliant to all study-related procedures including timely completion of all the efficacy assessments (e.g., RiiQ/other PRO questionnaires) up to Day 35 (see [Schedule of Activities](#)).

When participants are hospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the [Schedule of Activities](#), if practically feasible.

If the reason for discontinuation of study intervention is full withdrawal of consent, refer to Section 7.2.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered to ensure sufficient evaluable participants for the primary analysis.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent.
- Death.
- The participant is poorly compliant with completing ePRO questionnaires, preferably after evaluation and discussion between the investigator and the sponsor.
- The participant is poorly compliant with other study procedures, study intervention administration, visits, and assessments, preferably after evaluation and discussion between the investigator and sponsor.
- Decision by the sponsor to stop or cancel the study.
- Decision by the investigator to withdraw participant.
- Decision by local regulatory authorities or Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) to stop or cancel the study.

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

If a participant however withdraws consent to further continue in the study, he or she will also be offered an optional Safety Follow-up Visit. The optional follow-up visit will occur the day of consent withdrawal or the day after and will consist of the same assessments as the Final Study visit (Day 35).

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent for further study participation, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

In case the participant withdraws consent during the treatment or follow-up phase, an optional Safety Follow-up visit will be offered.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 10.3). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

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

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The [Schedule of Activities](#) summarizes the frequency and timing of efficacy, safety, and PK/pharmacodynamic (PD) measurements, as well as PRO, biomarker analysis, and MRU, applicable to this study.

Clinical course and severity of RSV infection will be assessed through different measures (see Section 8.1.1). Severity and evolution of symptoms will be assessed using the RSV symptom assessments described in Section 8.1.1.1. Progression of RSV disease will be assessed using a complication endpoint (8.1.1.2). Health-related quality of life (HRQOL) and functioning assessments reported by participants are described in Section 8.1.2. Furthermore, assessment of antiviral activity and viral sequencing is described in Sections 8.1.3 and 8.1.4, respectively.

If a participant is clinically stable and there is no safety concern, it is recommended that ePRO assessments as well as scheduled on-site visits are performed before use of any concomitant medication(s) for symptom relief (e.g. bronchodilators, cough medication).

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ePRO, ECG, vital signs, bilateral nasal mid-turbinate swab, blood sampling, physical examination, and CSS. It is recommended that the vital signs are assessed after the participant has rested for at least 15 minutes. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation and eCRF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

All ePRO assessments should preferentially be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses, except for the screening assessment, which can take place after investigator assessment of eligibility. Refer to the ePRO completion guidelines for instructions on the administration of ePROs.

As ePRO assessments are required for the primary efficacy evaluation, if no translation is available in a language in which the participant is fluent, the participant cannot be enrolled in the study.

The ePRO device (this can be provided by the site to the participants at screening, or participants can bring their own device) will be used to record participant's ratings of the severity of their symptoms and changes in their functioning and HRQOL every day (once daily or twice daily), as specified in the [Schedule of Activities](#). Electronic PRO assessments will be completed by all participants on the ePRO device, in a language in which the participant is fluent. Translations have been performed for all PRO assessments using recommended best practices for PRO research ([Wild 2009](#)).

The investigator/study personnel will provide sufficient information (included in the study manual and participant information guide) to enable the participants to complete the ePRO on the device correctly and on schedule to avoid missing or incorrect data. Prior to completing the screening assessment, the participant must complete a training module (included on the ePRO device) on how to enter responses to questions on the ePRO device. If a participant requires assistance entering responses in the ePRO device, a caregiver or member of the study team who is trained can interview the participant and enter the participant's responses on the ePRO device on the participant's behalf.

ePRO completion compliance should be assessed daily by the study site personnel via the ePRO vendor portal. If scheduled assessments are missing from the prior day, the sites will contact the participant to identify reason for missing PRO and document reasons for missing PRO assessments in the eCRF based on discussion with the participant.

On Day 28, all participants will be contacted by the study site personnel for a telephone follow-up visit to assess the clinical status and MRU and to check for any AEs including RSV-related complications.

On Day 35 (ie, the last study-related visit), a telephone follow-up will be performed with all participants to assess the clinical status and MRU and check for RSV-related complications. In addition, they will be asked to return the ePRO device to the site by courier in case no visit is planned. Alternatively, if an on-site visit is required, the ePRO device can be returned at the study visit.

In case participants have ongoing AEs or other ongoing laboratory, vital signs or ECG-related abnormalities at time of the Day 28 and Day 35 follow-up visit, participants might be requested, at the discretion of the investigator, to have a safety follow-up visit at the site if feasible (see Section 9.4.4 for more details on safety assessments).

Medications taken will be discussed with the investigator and recorded on the concomitant medication page of the eCRF.

Safety and tolerability, including AEs, laboratory assessments, ECGs, vital signs, and physical examination will be assessed throughout the study from signing of the main ICF until the participant's last study-related activity (see Section 8.2).

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a popPK model (see Section 8.4).

Blood samples collected for biomarker research may be used for biomarker research analyses (see Section 8.5).

The presence of other respiratory viruses or bacteria in the nasal mid-turbinate swab samples will be assessed as described in Section 8.6.

Medical resource utilization data will be collected. Refer to Section 8.7 for details.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the [Schedule of Activities](#) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples

must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Blood Sample Collection and Handling

The maximum amount of blood drawn from each participant in this study over the duration of the study (maximum approximately 60 mL) is considered to be acceptable for the population in this study.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. This could increase the total blood volume.

Nasal Sample Collection and Handling

For the evaluation of antiviral activity, the RSV viral load in bilateral nasal mid-turbinate swabs will be measured at the central laboratory using a qRT-PCR assay (see Section 8.1.3). Viral sequencing will also be performed on the bilateral nasal mid-turbinate swabs (see Section 8.1.4). Only nasal mid-turbinate swabs provided for this study may be used. Other swabs are not acceptable for specimen collection as they may inhibit recovery of the pathogens. Note that in case of supply issues for nasal mid-turbinate swabs because of increased demand due to the COVID-19 pandemic, alternative nasal swabs instead of nasal mid-turbinate swabs may be provided for nasal sample collection for the study assessments.

The presence of viral (other than RSV) or bacterial co-pathogens will be assessed in the bilateral nasal mid-turbinate swab sample by using multiplex PCR at the central laboratory (see Section 8.6).

Refer to the [Schedule of Activities](#) for the timing and frequency of all sample collections.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Rilematovir JNJ-53718678 IB and any addenda.
- Laboratory manual.
- IWRS Manual.
- ePRO instruction/training guidelines.
- Electronic device for ePRO assessments.
- eCRF completion guidelines.
- Specimen collection kits for PK, safety blood and urine samples, and bilateral nasal mid-turbinate swabs together with universal transport medium tubes (for use on-site and at home).
- Materials for transport of nasal swab samples taken at home (eg, cool packs, biohazard packs, ...).

- Contact information page(s).
- ECG machine and manual.

8.1. Efficacy Assessments

- The PRO instrument will be provided in the local language(s) in accordance with local guidelines.
- The PRO and AE data will not be reconciled with one another.

8.1.1. Clinical Course and Severity of RSV Infection

Clinical evaluation includes vital sign assessments (ie, body temperature, respiratory rate, pulse/heart rate, peripheral capillary oxygen saturation [SpO₂]) and physical examination assessments (ie, presence of wheezing or crackles/rhonchi) as measured during site visits. Clinical evaluation also includes evaluation of the occurrence of AEs, RSV-related complications, and need for medications (including antibiotics).

Furthermore, the following evaluations of the clinical course of RSV infection will be performed for all participants, according to the time points indicated in the [Schedule of Activities](#).

8.1.1.1. RSV disease symptoms

All participants will assess the severity and/or duration of symptoms of RSV disease in the ePRO device using the RiiQ™ Symptom Scale (see Appendix 10.11.1), the Pre-Existing Symptom Questionnaire (see Appendix 10.10), and 2 Patient Global Impression (PGI) questions about the overall severity and change in RSV disease: PGI of severity (PGI-S) (see Appendix 10.12) and PGI of change (PGI-C) in RSV disease (see Appendix 10.13). In addition, the investigator will evaluate participants to complete the CSS questionnaire (see Appendix 10.18).

RiiQ™ Symptom Scale

To evaluate the impact of rilematovir treatment on RSV disease severity and duration, participants will rate the severity of the 13 most common symptoms in adults ([Falsey and Walsh 2000](#)) by completing the RiiQ™ Symptom Scale and rating the worst severity of their RSV symptoms from screening/baseline through the Day 14 visit for the past 12 hours twice daily (AM/PM), and from Day 15 through Day 35 once daily for the past 24 hours on the ePRO device.

Participants rate each RSV symptom on a scale from None (0), Mild (1), Moderate (2), to Severe (3):

- 6 Respiratory Tract Symptoms:
 - URTD symptoms: sore throat and nasal congestion
 - LRTD symptoms: cough, wheezing, coughing up phlegm (sputum), and short of breath
- 7 Systemic Symptoms: headache, feeling feverish, body aches and pains, fatigue (tiredness), neck pain, interrupted sleep, and loss of appetite.

The RiiQ™ Symptom Scale is one of 4 scales in the RiiQ™, a 29-item PRO measure developed for evaluating severity of symptoms of an acute respiratory infection (RiiQ™ Symptom Scale) and the impact of a respiratory infection on 3 domains of functioning and HRQOL (RiiQ™ Impact Scales). Additional information on the 3 RiiQ™ Impact Scales is provided in Section 8.1.2.

Evidence from the analysis of a longer symptom assessment used in a Phase 2 study identified 7 Key RSV Symptoms that were most informative about severity and recovery from RSV symptoms in a small study of adults treated in a community setting (Study 53718678RSV2004). Those analyses confirmed that collection of other symptoms beyond the 7 Key RSV Symptoms provided little or no additional information about time to recovery of moderate to severe symptoms of RSV disease. The same Key RSV Symptoms were best able to differentiate mild from moderate or severe RSV disease reported by older adult participants who developed RSV infection during an RSV vaccine study (Yu 2020).

Symptoms in the RiiQ™ Symptom Scale will be evaluated individually, as 2 subscales (Respiratory Tract Symptoms and Systemic Symptoms) and as the 7 Key RSV Symptoms. Analyses will evaluate mean scores and recovery to pre-existing severity levels based on symptoms reported at screening on the Pre-Existing Symptom Questionnaire.

Pre-Existing Symptom Questionnaire

The Pre-Existing Symptom Questionnaire was adapted from the RiiQ™ Symptom Scale for this study to enable evaluation of recovery from an RSV infection in adults with chronic comorbid illness that include respiratory or systemic symptoms similar to those caused by an RSV infection. It consists of the same 13 symptoms as assessed in the RiiQ™ Symptom Scale but asks participants to describe only those symptoms present prior to the onset of their current illness due to RSV infection (see Appendix 10.10). Participants will complete the Pre-Existing Symptom Questionnaire at screening after they complete the RiiQ™ Symptom Scale to enable evaluation of eligibility for the study and efficacy of treatment.

Patient Global Impression of RSV

Patient Global Impression of Severity (PGI-S) is a global rating of how severe the participant's respiratory infection symptoms at their worst scored that day on a 1-point ordinal scale with responses ranging from No symptoms today (0) to Very Severe (4) (see Appendix 10.12). It will be used not only to provide a general impression from the participant's perspective on the severity of RSV disease, but also to establish guides for interpreting how much change on other PRO endpoints can be considered clinically meaningful (Revicki 2008).

Participants will rate the severity of their RSV-related disease using the PGI-S once daily from screening/baseline through the Day 35 visit.

Patient Global Impression of Change in Severity (PGI-C) is a single item PRO aimed to capture the participant's perceptions of improvement or deterioration in the severity of RSV symptoms compared to before the participant started taking the study intervention, important for monitoring

when a clinically important change in the participant's health has occurred based on the participant's own perspective. A simple 7-point ordinal response scale for the PGI-C provides a range from much better (3), about the same (0), to much worse (-3) (see Appendix 10.13).

Clinician Symptom Score

The RSV2008 study aims to evaluate the treatment effect of rilematovir in participants with moderate RSV disease and are enrolled based on the presentation of at least 2 LRTD symptoms, one of which needs to be at least moderate due to RSV infection. The CSS was therefore adapted to focus on the LRTD signs/symptoms and will be studied as an exploratory study objective (see Appendix 10.18).

To evaluate the impact of rilematovir treatment on RSV disease severity, clinicians will rate the severity of the RSV LRTD sign/symptoms in the study participants by completing the CSS questionnaire from screening/baseline through Day 35 as specified in the [Schedule of Activities](#).

Five RSV LRTD sign/symptoms will be rated on a scale from None (0), Mild (1), Moderate (2), to Severe (3):

- Cough, short of breath, wheezing, coughing up phlegm (sputum), presence of rales/rhonchi/crackles

This clinician rated assessment of RSV disease severity will be based on the information on an individual participant (history, underlying comorbidity, baseline disease characteristics), overall clinical evaluation as well as interview of the participants on their symptoms. During each assessment, clinician will select the level that most accurately describes the severity of the participant's symptoms. The clinician then indicates the score for each item in the 'score' column provided.

8.1.1.2. Complications of RSV infection

Treatment comparisons will evaluate the potential of rilematovir to reduce the incidence and severity of complications with onset after treatment initiation that are associated with RSV disease.

Complications (including all RSV-related pulmonary and extrapulmonary complications) will be determined based on predefined criteria taking into account the investigator's assessment of available clinical data (eg, chest X-ray results, lab results) and will be documented as AEs in the eCRF.

- Pulmonary complications are defined as:
 - Primary viral pneumonia: a progressive event involving the lower respiratory tract with bilateral and/or diffuse radiological findings. No bacterial agent is identified in sputum cultures.
 - Bronchitis.
 - Respiratory failure: defined as either hypoxemic respiratory failure characterized by an arterial oxygen tension (PaO₂) lower than 60 mmHg with a normal or low arterial carbon

dioxide tension (PaCO_2), or hypercapnic respiratory failure characterized by a PaCO_2 higher than 50 mmHg.

- Secondary bacterial pneumonia (including pneumonia attributable to unusual pathogens): a clinical event compatible with lower respiratory tract involvement, with lobar infiltrates on radiological studies and/or microbiological isolate of a bacterial pathogen, including unusual pathogens in sputum cultures.
- Exacerbations of underlying chronic pulmonary diseases such as COPD and asthma: participants with documented medical history of COPD or asthma with a sudden worsening of symptoms and deteriorating respiratory function (the latter as evidenced by worsening hypoxia, tachypnea, etc.). The event must start before a full recovery from the RSV infection occurred.
- Extrapulmonary complications are defined as:
 - Cardiovascular and cerebrovascular disease events (eg, myocardial infarction, atrial fibrillation, stroke).
 - Acute heart failure or exacerbation of underlying CHF: participants with documented medical history of CHF with a sudden worsening of symptoms and deteriorating respiratory function.
 - Acute exacerbation of chronic kidney disease (CKD).
 - Severe dehydration.
 - Decompensation of previously controlled diabetes mellitus.
 - Other respiratory infections.

8.1.1.3. Other measures of RSV-related disease progression

Respiratory therapeutic interventions associated with RSV-related disease progression after the start of rilematovir treatment will be evaluated by the proportion of participants with new antibiotic use, or new or increased use in bronchodilator/nebulizer, systemic corticosteroids, or home oxygen supplementation up to Day 35. In addition, any medical attendance for the respiratory infection after the start of rilematovir will be assessed by the proportion of participants with unscheduled outpatient clinic visits, emergency room visits or hospitalization for respiratory infection (MARIs) during the study period up to Day 35.

8.1.2. Functioning and Health-related Quality of Life

Although RSV disease usually resolves within a few weeks, the morbidity caused by respiratory and systemic symptoms can make it difficult for people to do things they would ordinarily do, and cause worry about how long the illness will last and how much they are dependent on or burdening others close to them ([Osborne 2011](#), [Scott 2018](#)).

The impact of treatment on the degree to which RSV symptoms interfere with the participant's routine functioning and HRQOL will be assessed by all participants in the ePRO device using the the Hours Missed from Work question (see Appendix 10.17; this question will only be asked if the participant or on other member of his household is employed [see Appendix 10.16]), the RiiQ™

Impact Scales (see Appendix 10.11.2), the Return to Usual activities question (see Appendix 10.14), the Return to Usual Health question (see Appendix 10.15), and the 5-level EuroQol® 5-Dimension (EQ-5D-5L) questionnaire (see Appendix 10.19), at the timepoints specified in the [Schedule of Activities](#).

Hours Missed from Work

Participants who indicate during the first Day 1 assessment that at least one person in their household was employed will be asked to report the total number of hours missed from work by all members of the participant's household, including the participant, due to RSV (see Appendix 10.16 and Appendix 10.17). The participant will complete this question on the ePRO device at the timepoints specified in the [Schedule of Activities](#). This question was created for this study to help address the paucity of information on the impact RSV in adults on hours missed from work.

Respiratory syncytial virus, like most acute respiratory infections, can result in debilitating illness that causes patients or their family members who care for them to miss time from work ([Tsai 2014](#)).

Much of the research on the impact of RSV on work loss and productivity has focused more on the parents of young children with RSV. In adults, high risk of severe RSV disease is well documented for older adults who may no longer be in the workforce but may require support from a family member during their illness has not been extensively studied ([Falsey and Walsh 2000](#)). However, one study of 10 healthy hospital staff with natural RSV infections found that 8 of 10 missed work for an average of 6 days due to their RSV disease ([Hall WE 1978](#)). Until recently, diagnostic testing in adults to discriminate viral pathogens has generally been limited to screening for influenza. As testing for COVID-19 and other viruses increases, the research on work-related impact of RSV in adults is expected to increase. Evidence from the current study is expected to add to this growing body of evidence of the economic burden of RSV disease on patients and their families.

RSV-specific HRQOL

To understand the impact of an acute episode of RSV infection on participant's daily lives, participants will report on their functioning and disease specific HRQOL using the 3 RiiQ™ Impact Scales (see Appendix 10.11.2):

- ***RiiQ™ Impact on Daily Activities Scale (RiiQ™DAS)*** that asks about any difficulty that participants may have had performing 7 activities of daily living (get out of bed, prepare meals, perform usual activities, leave the home, concentrate on tasks, take care of self, and go out of the room you are in) using the response options No difficulty (0), Some difficulty (1), Moderate difficulty (2), and Great difficulty (3).
- ***RiiQ™ Impact on Emotions Scale (RiiQ™IES)*** that asks participants to report on impacts to 4 specific moods and emotions (irritable, helpless, worried, and frustrated) using the response options Not at all (0), Somewhat (1), Moderately (2), and Extremely (3).

- ***RiiQ™ Impact on Others Scale (RiiQ™-IOS)*** that asks participants to indicate the extent to which they have been concerned about 5 specific social and interpersonal impacts (people worrying about you, being a burden, people being annoyed with you, needing to depend on people, and people having to do extra things for you) using the response options Not at all concerned (0), Somewhat concerned (1), Moderately concerned (2), and Extremely concerned (3).

The RiiQ™ Impact Scales can be administered individually or together with or without the RiiQ™ Symptom Scale as required for the study setting. Each scale takes less than 2 minutes to complete.

Evidence to support the adequacy of the development and validation of these scales for studies in adults with influenza-like illness has been described ([Osborne 2011](#)) and their use for understanding the impact of influenza on older adults has been reported ([van Essen 2014](#)).

Participants will complete the RiiQ™ Impact Scales on the ePRO device once daily in the evening (PM) from Day 1 (as close as possible and before the first study intervention administration) through the Day 35 visit.

Analyses will evaluate change over time in RiiQ™ Impact Scale scores computed as the mean of the items for each scale.

Generic HRQOL and Health Utilities

To enable comparison of the impact of RSV treatment on HRQOL as compared to HRQOL reported in the general population or in treatments for other medical conditions, participants will rate their HRQOL using the generic EQ-5D-5L at baseline, Day 3, Day 14, and Day 21 visits (see [Schedule of Activities](#) and Appendix 10.19). The EQ-5D-5L takes only 2-3 minutes to complete.

EQ-5D-5L was developed to be applicable to a wide range of health conditions and treatments as a brief, simple assessment of health status. It includes 6 cognitively undemanding questions that provide a profile on 5 HRQOL domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Domains can be analyzed descriptively as separate outcomes or combined in a single index of health status that can be used in the clinical and economic evaluation of health care. In addition, EQ-5D-5L contains a visual analog scale (VAS) asking participants ‘how good or bad is your health TODAY’ on a scale with endpoints labeled ‘the best health you can imagine’ and ‘the worst health you can imagine’ that provides a quantitative measure of overall health as judged by the individual participants ([Reenan 2015](#)).

EQ-5D-5L is designed for self-completion either on electronic devices or using paper-and-pencil questionnaires and can be administered as an interview either face-to-face or by telephone. Instructions to participants are included in the questionnaire, and separate instructions for interview administration are provided.

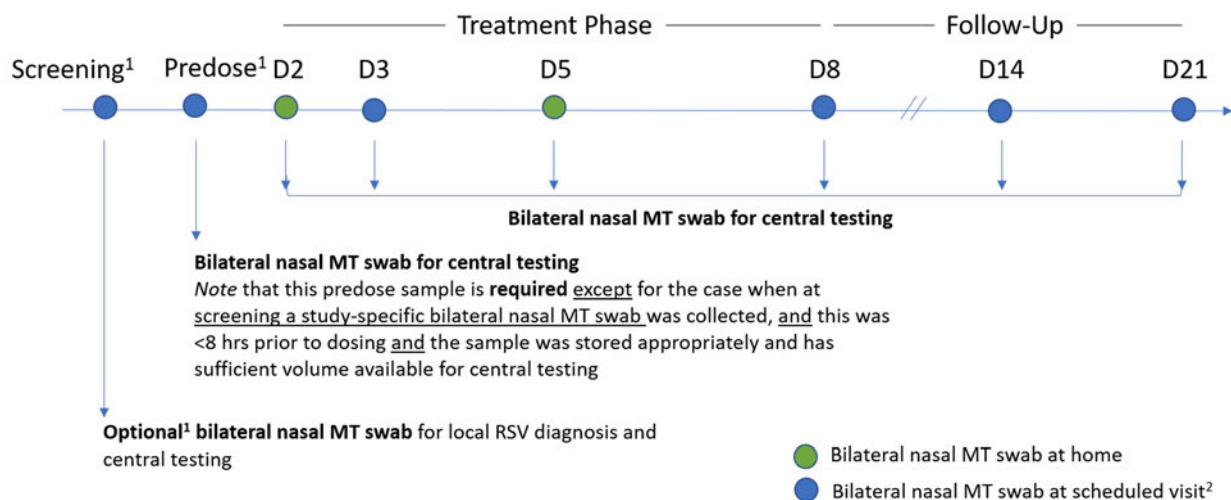
8.1.3. Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal secretions, obtained via a bilateral nasal mid-turbinate swab sample, will be measured at the central laboratory using a qRT-PCR assay. The qRT-PCR used to determine RSV viral load will also provide information on the RSV subtype. Bilateral nasal mid-turbinate swab specimens for the determination of RSV viral load will be collected at several time points during the study as indicated in the [Schedule of Activities](#). A nasal mid-turbinate swab should be collected from each nostril and both swabs should be put in the same universal transport medium tube (ie, a bilateral nasal mid-turbinate swab sample). Only at times when sampling of both nostrils is not feasible, such as in case of bleeding in one nostril, one nasal mid-turbinate swab should be collected from one nostril (ie, the non-bleeding nostril).

The baseline bilateral nasal mid-turbinate swab should be collected as close as possible and prior to the first administration of study intervention (on Day 1). If a study-specific screening bilateral nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline predose sample, provided that the study-specific screening bilateral nasal mid-turbinate swab sample was stored appropriately and has sufficient sample volume available (volume is considered sufficient if no more than 600 µL from the original sample has been used for local RSV testing and the entire remainder of the original sample is available). Only in such case, no additional sample needs to be collected at Day 1 predose. The next swabs should be collected preferably at approximately the same time as on Day 1 each day (see [Schedule of Activities](#)). During scheduled visits on Day 3, Day 8, Day 14 and Day 21, bilateral nasal mid-turbinate swabs will be collected by a health care practitioner. On Day 2 and Day 5, bilateral mid-turbinate nasal swabs are collected at home preferably by a health care practitioner and, only if not possible by an health care practitioner, by the participant (or his/her spouse, partner, relative, or other caregiver) after being properly trained by the investigator/study-site personnel ([Figure 3](#)). In case preferred by the participant, all bilateral mid-turbinate swabbing may also be performed at the site. The collection of these nasal swabs and date and time of sampling should be recorded for all participants in the eCRF. All participants will be given appropriate nasal mid-turbinate swabs and universal transport medium (same supplies as those used to collect nasal samples at the sites) to collect nasal mid-turbinate swabs. All swabs collected at home should be stored immediately between 2°C and 8°C (in the refrigerator) and brought to the site at the latest at the Day 3 and the Day 8 visit.

Figure 3: Schedule for Collection of Bilateral Nasal Mid-Turbinate Swab Samples

Figure: Schedule for Collection of Bilateral Nasal MT Swab Samples

¹ Screening and predose should preferably occur on the same day.² Not required if positive RSV result from **local SOC sample** can be used for eligibility (collected within 24 hrs prior to start of screening)³ If feasible, home visits are allowed instead of on-site visits, during which the bilateral nasal MT swab is collected by an HCP at home.

D: Day, hrs: hours, min: minimum, MT: mid-turbinate, RSV: respiratory syncytial virus, SOC: standard-of-care.

Additional information about the collection, handling, and shipment of biologic samples can be found in the laboratory manual.

Changes in viral load will be evaluated but will not be reported as AEs.

8.1.4. Viral Sequencing

Viral resistance will be monitored by sequencing of the RSV F gene in all baseline samples and in post-baseline samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at the request of the sponsor's virologist. Sequencing results may be presented in a separate report. Sequencing data will not be reported to the investigators.

Changes in viral sequence will be evaluated but will not be reported as AEs.

8.2. Safety Assessments

Details regarding the IDMC are provided in Committees Structure in Appendix 10.3. The PRO and AE data will not be reconciled with one another.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Appendix 10.4.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the [Schedule of Activities](#).

8.2.1. Physical Examinations

A complete physical examination (including height and body weight measurements) will be performed at screening. A targeted physical examination will be performed at the other site visits (see [Schedule of Activities](#)) and includes evaluation of body weight (Day 21 only), the respiratory system, nose, ear, throat, and facial and neck lymph nodes.

Any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF. Clinically relevant findings present at screening will be reported as medical history, any worsening of these findings during the study must be reported as an AE.

8.2.2. Vital Signs

Body temperature, pulse/heart rate, respiratory rate, and SpO2 will be assessed as part of the clinical parameters (see Section [8.1.1](#)). Additional vital signs assessments include systolic blood pressure and diastolic blood pressure. It is recommended that the vital signs are assessed after the participant has rested for at least 15 minutes.

Blood pressure and pulse/heart rate measurements will be assessed in a sitting or supine position (same position at each measurement) with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

Twelve-lead ECGs will be collected at the time points specified in the [Schedule of Activities](#) and when clinically indicated or to confirm abnormal ECG findings.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

If multiple assessments are scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ePRO, ECG(s), vital signs, bilateral nasal mid-turbinate swab, blood sampling, physical examination, and CSS.

Central ECG readings will be performed by a central ECG laboratory. Instructions for ECG acquisition and ECG transmission will be described in the manual provided by the ECG laboratory. There will be 2 ECG reports: a preliminary report and a final report. Both ECG reports generated by the central ECG lab will need to be interpreted for clinical significance, signed and dated by the investigator, and filed in the participant's medical record. Clinically relevant abnormalities emerging during the study should be recorded by the investigator in the AE section of the eCRF.

For eligibility determination, the machine read ECG results, printed on the ECG device print-out of the ECG tracing, will be used. If post-baseline, a participant has a QTcF interval value ≥ 500 ms based on the machine read QTcF value, confirmation needs to be obtained as soon as possible during the same visit by another machine read ECG. If confirmed, the participant needs to be withdrawn from study intervention (see also Section 7.1) and additional ECGs need to be performed daily until resolution of the QTcF interval prolongation is confirmed (see also Section 8.3.7.2). In case other clinically relevant abnormalities are observed post-baseline, a confirmatory ECG must be performed preferably within 48 hours, but no later than 72 hours, after the results have become available. Evaluation of clinical relevance should be done on confirmed results.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected as noted in Appendix 10.2. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. If a participant has a laboratory abnormality that meets the liver safety management discontinuation criteria (see Appendix 10.6), the participant should be permanently discontinued from the study intervention and the study. If a participant has any other Grade 3 or Grade 4 laboratory abnormality during the treatment period, confirmation needs to be obtained by a repeat test (local lab), to be performed within 48 hours of the result being available at the site. Please refer to the study intervention discontinuation guidance in Section 7.1.

8.2.5. Pregnancy Testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study (see [Schedule of Activities](#)).

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaint (PQC), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Complications associated with RSV disease as listed in Section 8.1.1.2 are considered events of interest. Additional data related to these events are collected when available and will be captured separately in the eCRF.

Anticipated events for this study are defined in Appendix 10.9 and will be recorded and reported as described in Section 8.3.4.

Further details on AEs, SAEs, and PQC can be found in Appendix 10.4.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Anticipated events will be recorded and reported as described in Appendix 10.9.

For participants having signed a diagnostic ICF only (ie, who do not enroll in the study by signing the main ICF), only study procedure-related AEs will be reported.

Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the SAE form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events including those related to pregnancy outcomes will be followed by the investigator as specified in Appendix 10.4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE (serious or non-serious) that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the SAEs that will be considered anticipated events are listed in Appendix 10.9.

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment Committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Because the study intervention may have an effect on sperm, pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Symptoms of RSV disease, as reported in the RiiQ™, will not be reported as AEs but constitute a part of the efficacy evaluations. However, they will be reported as (S)AE if they are considered related to the study intervention or fulfill the SAE definition.

The terms “disease progression” and “complication of RSV” should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression (including complications) will be reported as AE or SAE terms (refer to AE Definitions and Classifications in Appendix 10.4).

8.3.7. Safety Areas of Evaluation

8.3.7.1. Safety Topic of Special Interest: Hepatobiliary effects

Refer to Appendix 10.2 for protocol-required safety laboratory assessments. The severity grade of laboratory abnormalities in liver function tests is assessed using the criteria specified in the Division of Microbiology and Infectious Diseases (DMID) Toxicity Table (see Appendix 10.7). Refer to Appendix 10.6 for suggested actions and follow-up assessments in case of abnormal liver function in participants with normal liver function at screening. Ad hoc assessments (such as alkaline phosphatase, international normalized ratio [INR], gamma-glutamyl transferase [GGT]) may be performed at the discretion of the investigator, during unscheduled visits.

A liver safety management plan is implemented which is based on screening results after the laboratory results become available to the site (see Appendix 10.6).

For any Grade 3 or 4 laboratory abnormalities that occurred at Day 7/8, and Day 21 visits, participants should have a confirmatory measurement via the central lab, preferably within 48 hours after the laboratory results become available to the site. For confirmed Grade 3 or 4 laboratory abnormalities, participants should be followed until resolution (return to baseline) or stabilization of liver enzymes (ALT, aspartate aminotransferase [AST], bilirubin) elevation. During the study, these assessments will be captured as unscheduled assessments/visits.

8.3.7.2. Cardiac events potentially related to QT prolongation

Regular cardiac safety monitoring will be done in this study via assessments of AEs, laboratory abnormalities, and regular ECGs as per the [Schedule of Activities](#).

A participant's study intervention must be discontinued if the participant has a confirmed QTcF interval value ≥ 500 ms at any scheduled visit based on the machine read QTc value. Confirmation needs to be obtained immediately by another ECG machine read, locally at the site (see Section 7.1).

For participants with a confirmed QTc interval value > 500 ms, the following measures should be taken:

- The cardiac event must be reported to the sponsor within 24 hours.

- The investigator should request urgent cardiology referral, within 24 hours if possible.
- Clinical evaluation including safety biochemistry (such as electrolytes), assessment of the use of concomitant QT prolonging drugs, and evaluation for the presence of any structural heart disease must be conducted. Levels of potassium and magnesium to be determined by the local and by the central laboratory at the timepoint specified in the [Schedule of Activities](#).
- In case of hypokalemia and/or hypomagnesemia at screening or at any of the visits in the study period, the levels of potassium and magnesium should be corrected by taking into account any underlying condition and as soon as possible to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required.
- An ECG should be repeated (central ECG) every 24 hours until resolution of QTcF interval prolongation is confirmed. The participant's condition should be followed until resolution (return to baseline) or stabilization. During the study, these assessments will be captured as unscheduled assessments/visits.

For participants with a laboratory abnormality of hypokalemia of <2.5 mEq/L and/or hypomagnesemia of <0.9 mEq/L in samples taken at screening or any time during the study intervention treatment period, following measures should be taken:

- Repeat to confirm the results (local test), to be performed within 24 hours of the result being available at the site.
- Participant's study intervention must be discontinued after confirmation of results.
- Clinical evaluation including assessment of cardiovascular status and ECG must be conducted.
- Electrolytes should be repeated every 24 hours until resolution is confirmed. The participant's condition should be followed until resolution (return to baseline) or stabilization. During the study, these assessments will be captured as unscheduled assessments/visits.

8.4. Pharmacokinetics

Blood samples will be used to evaluate the PK of rilematovir. Pharmacokinetic parameters will be determined using a popPK approach by means of nonlinear mixed-effects modeling. Blood samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Venous blood samples of approximately 2 mL per sample will be collected for measurement of plasma concentrations of rilematovir at time points indicated in the [Schedule of Activities](#). Samples can also be used for the analysis of metabolites of rilematovir, excipients, protein binding,

or endogenous markers for enzymes or transporters involved in the metabolism and distribution of rilematovir, at the discretion of the sponsor.

The following times need to be recorded: actual dates and times of study intervention administration on the day of the visit and the previous and the next day and actual dates and times of PK blood sampling. In addition, it should be documented whether the study intervention administration (ie, the one closest preceding the PK sample) is taken in fed state (ie, between 1 hour before and 1 hour after completion of a meal).

8.4.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of rilematovir and/or metabolites as applicable using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method by or under the supervision of the sponsor.

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Population PK analysis of plasma concentration-time data of rilematovir will be performed using nonlinear mixed-effects modeling. Based on the individual concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of rilematovir will be derived using popPK modeling, including, but not limited to: AUC, C_{trough} , and possibly C_{max} . Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant. Other PK parameters may be determined at the discretion of the sponsor if deemed useful to evaluate the PK of the analytes in scope. Data may be combined with those of other selected studies (ie, Phase 1 and 2 studies) to support a relevant structural model. The results of the popPK analysis will be reported in a separate report.

Data will be listed for all participants with available plasma concentrations per treatment arm. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention, missing information of dosing and sampling times, concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in a separate PK report.

Pharmacokinetic/Pharmacodynamic Evaluations

The PK/PD relationship of rilematovir exposure (AUC_{0-24h} , C_{max} , or C_{min}) with selected efficacy (change in viral load from baseline and clinical outcomes) and safety (including laboratory abnormalities and AEs) parameters will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the PK/PD analysis will be reported in a separate report.

8.5. Biomarkers

Blood samples for biomarker research will be collected at time points indicated in the [Schedule of Activities](#) and may be used for biomarker research (eg, host RNA, proteins including cytokines, cellular phenotyping), on the premise that these markers may play a role in the treatment response, safety or PK of rilematovir, or in RSV-related disease. Leftover nasal mid-turbinate swabs and blood samples collected for other testing may be used as well for the same purpose. Analyses of biomarkers will be conducted at the sponsor's discretion and may be reported separately from this study.

8.6. Detection of Baseline Presence of Other Respiratory Viruses or Bacteria

The presence of other respiratory viruses (other than RSV) or bacteria will be assessed in the bilateral nasal mid-turbinate swab sample collected at baseline (Day 1 predose or screening) by multiplex PCR at the central laboratory. Bilateral nasal mid-turbinate swabs from other time points may also be analyzed for detection of other respiratory viruses or bacteria, if deemed necessary.

8.7. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will be used to conduct secondary efficacy analyses (use of respiratory therapeutic interventions as well as medically attended visits) and may be used to conduct exploratory economic analyses. Medical resource utilization will include:

- Number and duration of medical care encounters (eg, increased nursing visits at home, emergency room [ER] visit).
- Number (proportion) of participants requiring hospitalization for respiratory/other reasons and duration of hospitalization (total days length of stay, including duration by wards; eg, ICU). In the event of hospitalization during the study, investigators must make every effort to collect details of hospitalization as feasible, including the reason and duration of hospitalization.
- Incidence of antibiotic treatment.
- Any new or increased use of systemic or inhaled corticosteroids and bronchodilators use.
- New or increased use of oxygen therapy.
- Duration of selected post-baseline (after start of study intervention) MRU.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy, safety, PK and PK/PD data are outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

As this an exploratory, hypothesis-generating study, no formal statistical testing will be performed.

9.2. Sample Size Determination

The study will aim to enroll approximately 180 participants in a 2:1 ratio to rilematovir 250 mg twice daily (approximately 120 participants) and placebo (approximately 60 participants).

The sample size calculation is based on the primary efficacy endpoint, which is the time to resolution of RSV LRTD symptoms from randomization up to Day 35 in the ITT-i analysis set.

With a sample size of 180 participants, there is an 80% probability to demonstrate a reduction of at least 20% in the primary efficacy endpoint when the true effect is 30%. As further guidance for the sample size of this study, the power to detect a treatment difference for the primary efficacy endpoint is also calculated.

An AFT model with underlying log-normal distribution for the time to resolution is assumed with a median in a placebo arm of 14 days and a scale parameter of 0.8 (as observed in Study 51738678RSV2004). Using the Gehan-Wilcoxon test to analyze the data and based on the assumptions that the time to recovery is improved by 30%, that approximately 10% of the total enrolled participants may not be centrally confirmed RSV positive, and that 5% of patients may drop out of the study early before reaching resolution of their RSV LRTD symptoms, a sample size of 180 participants (randomized in a 2:1 ratio to rilematovir 250 mg twice daily and placebo) will have an estimated power of 80% as based on 10,000 simulations using a 10% 2-sided significance level. The power was estimated as the number of simulated studies where the 2-sided p value from the Gehan-Wilcoxon test was <0.1 out of the 10,000 simulated datasets.

9.3. Populations for Analysis Sets

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

Analysis Sets	Description
Enrolled	All participants who sign the main ICF.
Randomized	All participants who were randomized in the study.
ITT-i	All participants who were randomized and treated (at least one dose) and had RSV infection confirmed by central laboratory analysis. Participants with confirmed SARS-CoV-2 infection (positive test by central laboratory analysis) are excluded. This analysis set will be used for the analysis of efficacy endpoints, as randomized.
Safety	All participants who took at least 1 dose of study intervention. This analysis set will be used for the analysis of safety endpoints, as treated.
Pharmacokinetic	All participants in the ITT-i set. Participants will be excluded from the PK analysis set if their data do not allow for accurate assessment of the PK parameters (eg, incomplete administration of the study intervention; missing information of dosing and sampling times).

9.4. Statistical Analyses

9.4.1. General Considerations

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.2. Participant Information

For all participants who received at least 1 dose of study intervention, descriptive statistics will be provided (safety analysis set).

All demographic (eg, age, height, weight, race, gender), other initial participant characteristics (physical examination, medical and surgical history, concomitant diseases), and RSV disease characteristics (eg, subtype, time since symptom onset) will be tabulated and analyzed descriptively by intervention group.

9.4.3. Efficacy Analysis

The primary analysis set for the efficacy analyses will be the ITT-i.

9.4.3.1. Primary endpoint

The primary endpoint is the time to resolution of RSV LRTD symptoms from initiation of study treatment up to Day 35 as assessed by the participant using the RiiQ™ Symptom Scale. The RSV LRTD symptoms are defined as the following symptoms from the RiiQ Symptom Scale: cough, short of breath, wheezing, and coughing up phlegm (sputum).

Resolution of RSV LRTD symptoms in participants without pre-existing conditions is reached when all RSV LRTD symptoms in the RiiQ Symptom Scale are scored as ‘None’ (score = 0) or ‘Mild’ (score =1) for at least 24 hours.

Resolution of RSV LRTD symptoms in participants with pre-existing conditions is reached when:

- Pre-existing symptoms that were worse at baseline have improved at least 1 point from baseline for at least 24 hours; and
- Pre-existing symptoms that were not worse at baseline have not worsened from baseline severity for at least 24 hours; and
- Symptoms that were not pre-existing at baseline should be scored as ‘None’ (score = 0) or ‘Mild’ (score =1) for at least 24 hours.

The primary efficacy endpoint will be estimated using an AFT model adjusted by the randomization factors (high-risk and time since symptom onset) and baseline RSV LRTD symptom domain score.

Kaplan-Meier curves as well as KM estimates of median time to resolution will also be provided.

9.4.3.1.1. Estimand

The primary estimand attributes are as follows:

- Population: outpatient adults (≥ 18 to ≤ 85 years of age) who are at high risk of RSV-related disease progression, with at least 2 LRTD symptoms due to RSV infection, with at least one of which needs to be at least moderate (if symptom did not pre-exist before

RSV onset), or is scored worse than usual (if symptom pre-existed before RSV onset) with time since symptom onset ≤ 72 hours, with RSV infection (based on local laboratory analysis), without SARS-CoV-2 infection (based on clinical diagnosis and/or local laboratory analysis). High-risk condition(s) for RSV-related disease progression is defined as:

- Presence of any of the underlying high-risk comorbid cardiopulmonary conditions (COPD, asthma, or CHF) AND/OR
- ≥ 65 years of age (elderly participants).

A. Study intervention:

- Rilematovir + SOC
- Placebo + SOC

B. Variable: time to resolution of RSV LRTD symptoms from initiation of study treatment up to Day 35.

C. Summary measure: ratio of treatment medians.

D. Intercurrent events and corresponding strategies:

Treatment discontinuation	Treatment policy strategy
Death	Composite strategy
Hospitalization	Treatment policy strategy
Major protocol deviation: missing more than 4 doses	Treatment policy strategy
Major protocol deviation: Use of prohibited medication	Treatment policy strategy
Use of symptomatic medication (e.g. bronchodilators): started or changed during treatment phase	Composite strategy
Respiratory viral co-infections (e.g. co-infection with SARS-CoV-2 (as per local laboratory, but not confirmed by central laboratory))	Treatment policy strategy
COVID-19 vaccination	Treatment policy strategy

9.4.3.2. Secondary clinical endpoints

The proportion of participants with complications (including all RSV-related pulmonary and extrapulmonary complications) from initiation of study treatment up to Day 35 will be analyzed using a logistic regression. Stratification factors will be added as covariates to the model. Similarly, all the secondary binary endpoints will be analyzed using a logistic regression.

All time-to-event secondary efficacy analyses will be analyzed similarly to the primary endpoint.

Changes from baseline over time as assessed by PRO questionnaires will be analyzed using a mixed-effect model with repeated measurements (MMRM). This analysis includes fixed categorical effects of treatment, randomization strata, time and treatment-by-time interaction, as well as the continuous covariates of baseline score and baseline score-by-time interaction.

9.4.3.3. Antiviral activity

Antiviral activity will be determined based on measurements of RSV viral load in nasal mid-turbinate swab samples by a qRT-PCR assay. These data will be analyzed graphically. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented.

Mean log₁₀ viral load values over time will be analyzed using MMRM. Differences between intervention groups in viral load, and the difference in the RSV viral load AUC through Days 3, 5, and 8 between intervention groups will be derived using appropriate contrasts deriving least square mean differences, including the 90% 2-sided confidence intervals.

The relationship between antiviral activity and baseline characteristics, including but not limited to RSV viral subtype and genotype will be explored.

9.4.3.4. Viral sequencing

The results of viral sequencing will be evaluated by the sponsor virologist. Pre-treatment genetic variations and relevant post-baseline changes in the RSV F gene (and other regions of the RSV genome, if applicable and on request of the sponsor virologist) will be tabulated and described. The effect of pre-treatment RSV F protein genetic variations and relevant post-baseline RSV F protein amino acid changes on antiviral response and/or clinical outcomes will be explored.

9.4.4. Safety Analyses

Safety data will be presented descriptively. For safety, baseline is defined as the last assessment prior to the first administration of study intervention.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the end of the study is considered to be treatment-emergent. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided (as defined in Appendix 10.7).

The laboratory abnormalities will be determined according to the criteria specified in the DMID adult toxicity table (as defined in Appendix 10.7) and in accordance with the normal ranges of the clinical laboratory if no gradings are available.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations and pre- vs post-intervention cross-tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

The ECG variables that will be analyzed are heart/pulse rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB), QT corrected according to Fridericia's formula (QTcF) (Bazett 1920, Hodges 1983, ICH 2005, Sagie 1992).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

The percentage of participants with ECG abnormalities will be tabulated by treatment.

Vital Signs

Descriptive statistics of respiratory rate, pulse/heart rate, SpO₂, body temperature, and blood pressure (systolic and diastolic) will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized by treatment.

9.4.5. Other Analyses

Pharmacokinetic Analyses

Pharmacokinetic analysis set of plasma concentration-time data of rilematovir will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics

(demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a PK analysis set plan and the results of the PK analysis set will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for rilematovir and included in the PK analysis set. Samples collected after the snapshot date will be analyzed at a later date and may be included in a PK re-analysis set when they become available after database lock.

Data will be listed for all participants with available plasma concentrations per intervention group. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

For each intervention group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters (ie, C_{trough} , C_{max} , and AUC_{0-12h}) including exposure information of rilematovir, and, if applicable, of metabolites and/or endogenous markers.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of rilematovir population-derived exposure parameters with selected antiviral activity parameters, clinical outcomes, and safety endpoints will be explored. These relationships will be presented in a tabular and/or graphical display. The results of the PK/PD analysis may be conducted at the sponsor's discretion and reported separately from this study.

Biomarkers Analyses

Statistical approaches to explore correlations between clinical outcome, viral load, and biomarkers in blood and nasal mid-turbinate swabs vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences among study participants. Analyses may be conducted at the sponsor's discretion and reported separately from this study.

9.5. Interim Analysis

An interim analysis may be conducted at sponsor's discretion when at least approximately 65% of participants are enrolled to allow preparation towards a Phase 3 study design. The interim analysis, performed by the sponsor in an unblinded manner, will preferably be conducted at the end of a northern or southern hemisphere RSV season.

9.6. Independent Data Monitoring Committee

An IDMC will be established as noted in Committees Structure in Section [10.3.6](#).

An IDMC will be established to monitor and review clinical safety data in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this study. The Committee will meet periodically to review safety data. After the review, the IDMC will provide recommendations regarding the continuation of the study to the Sponsor Committee, who will be responsible for decision making, considering the IDMC recommendation, and who will communicate these decisions to the study team.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

$\Delta\Delta Q_{TcI}$	placebo-corrected change from baseline for the individual-corrected QTc
AE	adverse event
AFT	accelerated failure time
ALT	alanine aminotransaminase
AST	aspartate aminotransferase
AUC	area under the curve
AUC _{0-12h}	AUC from time of administration up to 12 hours post dosing
AUC _{0-24h}	AUC from time of administration up to 24 hours post dosing
AUC _{0-96h}	AUC from time of administration up to 96 hours post dosing
AUC _{0-∞}	AUC from time of administration extrapolated to infinity
bid	bis in die; twice daily
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CSS	Clinician Symptom Score
C _{trough}	predose plasma concentration
CYP	cytochrome P450
ECG	electrocardiogram
eDC	electronic data capture
ER	emergency room
EQ-5D	EuroQol® 5-Dimension
F	fusion
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HP-β-CD	2-hydroxypropyl-beta-cyclodextrin
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT-i	intent-to-treat-infected
IWRS	interactive web response system
KM	Kaplan-Meier
LRTD	lower respiratory tract disease
MMRM	mixed-effects model with repeated measurements
MRU	medical resource utilization
OATP	organic anion transporting polypeptide
PaCO ₂	arterial carbon dioxide tension
paEC ₉₀	protein-adjusted 90% effective concentration
PBPK	physiologically-based pharmacokinetic(s)
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P glycoprotein

PK	pharmacokinetic(s)
popPK	population pharmacokinetic
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
qd	quaque die; once daily
q24h	every 24 hours
qRT-PCR	quantitative reverse transcription polymerase chain reaction
QTcF	QT interval corrected using Fridericia's formula
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	standard-of-care
SpO ₂	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
t _{max}	median time to reach maximum plasma concentration
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
URTD	upper respiratory tract disease
US	United States
VAS	visual analog scale

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation
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10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the [Schedule of Activities](#).

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	<u>Red Blood cell (RBC) Indices:</u> Mean Corpuscular Volume Mean Corpuscular Hemoglobin (MCH) MCH concentration	<u>White Blood Cell (WBC) count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Urea Total bilirubin (direct and indirect) Alkaline phosphatase Uric acid Creatinine Calcium Phosphorus Magnesium Glucose (preferentially fasting) eGFR _{crea}	
	Note: eGFR _{crea} to be calculated per CKD-EPI (Levey and Stevens 2010). Note: Levels of potassium and magnesium to be determined by the local and by the central laboratory. In case of confirmed hypokalemia and/or hypomagnesemia at screening, or at any of the visits in the study period, the levels of potassium and magnesium should be corrected also taking into account any underlying condition and as soon as possible to prevent cardiac disturbances.		
Routine Urinalysis	<u>Dipstick</u> Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	<u>Sediment^a (if dipstick result is abnormal)</u> RBC WBC Epithelial cells Crystals Casts Bacteria	
	^a At central laboratory		

	<p>If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.</p> <p>In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.</p>
Other Screening Tests	<ul style="list-style-type: none">• Urine pregnancy testing for women of childbearing potential only• Serology testing for HIV-1 and -2, hepatitis A, B & C• At screening, FSH will be tested for female participants who are amenorrheic for 12 months or less.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the participants).
- IB (or equivalent information) and amendments/addenda.
- Sponsor-approved participant recruiting materials.

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to participants.
- If applicable, new or revised participant recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention.
- New information that may adversely affect the safety of the participants or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants.
- Report of deaths of participants under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

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

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Prior to signing the main consent form for the study, participants may specifically allow for the collection and testing of nasal mid-turbinate swabs by signing the pre-screening (diagnostic) ICF if such testing is not SOC at the investigational site.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will

not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand rilematovir, to understand RSV infection, to understand differential intervention responders, and to develop tests/assays related to rilematovir and RSV infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1).

10.3.6. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor and review data for the study in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this study. The Committee will meet periodically to review the safety data. After the review, the IDMC will provide recommendations regarding the continuation of the study to the Sponsor Committee, who will be responsible for decision making, considering the IDMC recommendation, and who will communicate these decisions to the study team.

The IDMC will consist of at least 3 members, including one medical expert in respiratory infectious diseases, one cardiovascular expert knowledgeable about ECG readings, and at least one statistician knowledgeable about statistical methods for clinical studies and sequential analysis of study data. One of these individuals will chair the Committee. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

The committee will meet periodically to review the safety data. After the review, the IDMC will make recommendations regarding the continuation of the study. At any point during the study, the IDMC has the option to recommend modifications to the study conduct and/or to the safety assessments to the Sponsor Committee to ensure the safety of enrolled participants.

Sponsor Committee

A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making, considering the IDMC recommendations, and will communicate these decisions to the study team. Details are provided in the IDMC Charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding rilematovir or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The

investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of rilematovir, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and Substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the

version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory, and ECG and ePRO vendor into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to the eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by the study site personnel or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or another equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- History of smoking and all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
(The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may

require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For rilematovir, the expectedness of an AE will be determined by whether or not it is listed in the IB ([IB 2020](#)).

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity Grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).
Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The terms "disease progression" and complication of RSV should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Appendix 10.4).

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5, and Appendix 10.5.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:
USER-INDEPENDENT Highly Effective Methods That Are User-Independent <i>Failure rate of <1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Implantable progestogen-only hormone contraception associated with inhibition of ovulation^b • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ligation without reversal operation • Vasectomized Azoospermic partner (vasectomized or due to medical cause) (<i>Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.</i>)
USER DEPENDENT Highly Effective Methods That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – oral – intravaginal – transdermal injectable • Progestogen-only hormone contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – oral injectable • Sexual abstinence (<i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i>)
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of $\geq 1\%$ per year)
<ul style="list-style-type: none"> • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide^c • Cap, diaphragm, or sponge with spermicide • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)^c • Periodic abstinence (calendar, symptothermal, post-ovulation methods)

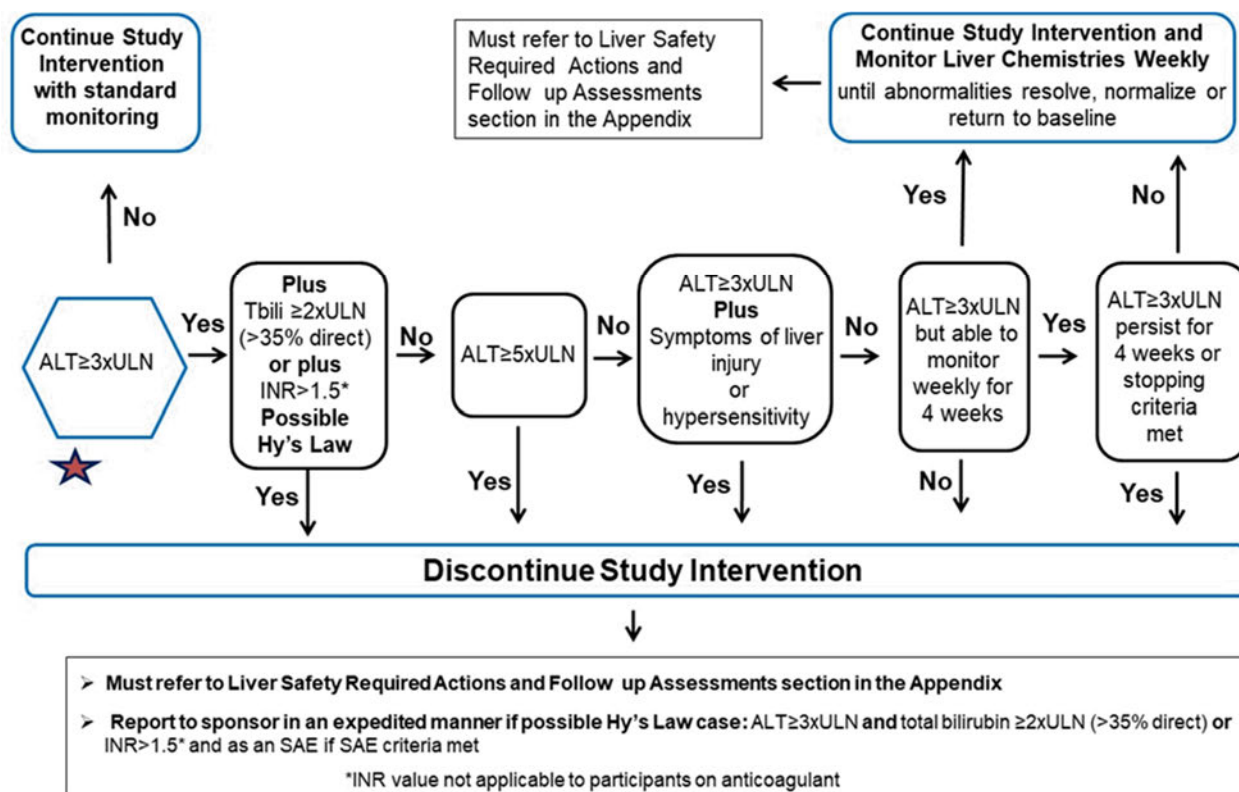
- | |
|---|
| • Withdrawal (coitus-interruptus) |
| • Spermicides alone |
| • Lactational amenorrhea method (LAM) |
| a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. |
| b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. |
| c) Male condom and female condom should not be used together (due to risk of failure with friction). |

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

A. STOPPING ALGORITHM

ALT ONLY: Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

10.7. Appendix 7: Toxicity Tables

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE (NIAID 2007) – NOVEMBER 2007

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal
 R_x = Therapy
 Mod = Moderate
 ADL = Activities of Daily Living

LLN = Lower Limit of Normal
 Req = Required
 IV = Intravenous
 Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

- GRADE 1 Mild** Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
- GRADE 2 Moderate** Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 Severe** Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 Life-threatening** Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used Toxicity Tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization [WHO]) have been adapted for use by the DMID and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1,000-1,500/ mm ³	750-999/ mm ³	500-749/ mm ³	<500/ mm ³
Platelets	75,000-99,999/ mm ³	50,000-74,999/ mm ³	20,000-49,999/ mm ³	<20,000/ mm ³
WBCs	11,000-13,000/ mm ³	13,000-15,000 / mm ³	15,000-30,000/ mm ³	>30,000 or <1,000 / mm ³
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	-----
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL -----	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ mL	41-50 mcg/ mL	51-60 mcg/ mL	> 60 mcg/ mL
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium <i>with</i> mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium <i>with</i> mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/ L	2.5 - 2.9 mEq/ L	2.0 - 2.4 mEq/ L or intensive replacement therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium <i>with</i> paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/l	> 7.0 mEq/ L or abnormal potassium <i>with</i> life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose <i>with</i> mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/d L	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose <i>with</i> ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium <i>with</i> life-threatening arrhythmia or tetany

CHEMISTRIES (continued)				
	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium <i>with</i> life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium <i>with</i> life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate <i>with</i> life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/d L	>15.0 mg/d L
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	>6 x ULN or dialysis required

ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS

	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR RBC casts	obstructive or required transfusion

CARDIOVASCULAR

	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrhythmia; hospitalization and treatment required
Hypertension	transient increase >20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	-----
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV1 of peak flow	requires treatment; normalizes with bronchodilator; FEV1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV1 25% - 50% of peak flow; or retractions present	cyanosis: FEV1 <25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring oxygen therapy

GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV flu ids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last <1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink flu ids; requires IV fluids

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, eg, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, eg, vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL

	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15mm	15-30 mm	>30mm	
Erythema	<15mm	15-30 mm	>30mm	
Edema	<15mm	15-30 mm	>30mm	
Rash at Injection Site	<15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	>40 C or >105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% cannot work	unable to care for self

10.8. Appendix 8: List of Commonly Used Medications With a Known Risk of QT Prolongation and Torsade de Pointes

Investigators must refer to the list of medications with known risk available at <https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf> (see copy below). Investigators must check regularly for any additions or updates to the list below.



The last revision date: December 17, 2020

See Note below for safe use of this Table



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Filters:
TdP Risk Category: Drugs with known TdP risk
Keyword:


Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Aclarubicin (Only on Non US Market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer	 	injection
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia	 	oral, injection
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia	 	oral
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)	 	injection
Astemizole (Removed from US Market)	Hismanal	Antihistamine	Allergic rhinitis	 	oral
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection	 	oral, injection
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)	 	oral
Cesium Chloride	Energy Catalyst	Toxin	Alternative therapy cancer	 	oral, injection
Chloroquine	Aralen	Antimalarial	Malaria	 	oral
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Nausea, Schizophrenia, many others	 	oral, injection, suppository
Chlorprothixene (Only on Non US Market)	Truxal	Antipsychotic	Schizophrenia	 	oral, injection
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication	 	oral
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection	 	oral, injection
Cisapride (Removed from US Market)	Propulsid	GI stimulant	Increase GI motility	 	oral
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression	 	oral
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection	 	oral, inhaled
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)	 	oral, nasal


Disopyramide	Norpace	Antiarrhythmic	Arrhythmia	 	oral, injection
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia	 	oral
Domperidone (Only on Non US Market)	Motilium, Motilium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting	 	oral, injection, suppository
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	 	oral
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia	 	oral
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea	 	injection
Erythromycin	E.E.S., Robimycin, EMyacin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abbotcin, Abbotcin-ES, Erycin, PCE Dispertab, Stiemycine, Aconasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility	 	oral, injection
Escitalopram	Cipralext, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI	Depression (major), anxiety disorders	 	oral
Flecainide	Tamboor, Almarytm, Apocard, Ecrinal, Flécaïne	Antiarrhythmic	Arrhythmia	 	oral
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection	 	oral, injection
Gatifloxacin (Removed from US Market)	Tequin	Antibiotic	Bacterial infection	 	oral, injection
Grepafloxacin (Removed from US Market)	Raxar	Antibiotic	Bacterial infection	 	oral
Halofantrine (Only on Non US Market)	Halfan	Antimalarial	Malaria	 	oral
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation	 	oral, injection
Hydroquinidine (Dihydroquinidine) (Only on Non US Market)	Serecor	Antiarrhythmic	Arrhythmia	 	oral
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti- inflammatory	Malaria, SLE, rheumatoid arthritis	 	oral
Ibogaine		Psychedelic	Narcotic addiction,		oral


(Only on Non US Market)			unproven	 	
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia	 	injection
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection	 	oral, injection
Levomepromazine (Methotrimeprazine) (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia	 	oral, injection
Levomethadyl acetate (Removed from US Market)	Orlaam	Opioid agonist	Narcotic dependence	 	oral
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva	Antipsychotic	Schizophrenia	 	oral, injection
Meglumine antimoniate (Only on Non US Market)	Glucantime	Antiparasitic	Leishmaniasis	 	injection
Mesoridazine (Removed from US Market)	Serentil	Antipsychotic	Schizophrenia	 	oral
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain	 	oral, injection
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection	 	oral, injection
Nifekalant (Only on Non US Market)	Shinbit	Antiarrhythmic	Arrhythmia	 	injection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting	 	oral, injection, suppository
Oxaliplatin	Eloxatin	Anti-cancer	Cancer	 	injection
Papaverine HCl (Intra-coronary)		Vasodilator, Coronary	Diagnostic adjunct	 	injection
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)	 	injection, inhaled
Pimozide	Orap	Antipsychotic	Tourette's Disorder	 	oral
Probucol (Removed from US Market)	Lorelco	Antilipemic	Hypercholesterolemia	 	oral
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia	 	injection
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia	 	injection
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia	 	oral, injection
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig,	Antibiotic	Bacterial infection	 	oral

	Roxar, Roximycin, Roxomycin, Rulid, Tirabacin, Coroxin				
Sertindole (Only on Non US Market)	Serdolect, Serlect	Antipsychotic, atypical	Schizophrenia, anxiety	 	oral
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia	 	inhaled
Sotalol	Betapace, Sotalax, Sotacor	Antiarrhythmic	Arrhythmia	 	oral
Sparfloxacin (Removed from US Market)	Zagam	Antibiotic	Bacterial infection	 	oral
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia	 	oral, inhaled
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia	 	oral, injection
Terfenadine (Removed from US Market)	Seldane	Antihistamine	Allergic rhinitis	 	oral
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor	Septic shock	 	injection
Terodiline (Only on Non US Market)	Micturin, Mictrol	Muscle relaxant	Bladder spasm	 	oral
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia	 	oral
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)	 	oral

 **Known Risk of TdP** - Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling.

 **Possible Risk of TdP** - Substantial evidence supports the conclusion that these drugs can cause QT prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

 **Conditional Risk of TdP** - Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation)

 **Drugs to Avoid in Congenital Long QT** - Substantial evidence supports the conclusion that these drugs pose a risk of TdP for patients with congenital long QT. Drugs on this list include those in the above three risk categories and other drugs that do not prolong the QT interval per se but they have a theoretical risk of causing arrhythmia that is based on their known stimulant actions on the heart.

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form.

Disclaimer and Waiver: The information presented is intended solely for the purpose of providing general information about health-related matters. It is not intended for any other purpose, including but not limited to medical advice and/or treatment, nor is it intended to substitute for the users' relationships with their own health care providers. To that extent, by use of this website and the information it contains, the user affirms the understanding of the purpose and releases AZCERT, Inc. from any claims arising out of his/her use of the website and its lists. The absence of drugs from these lists should not be considered an indication that they are free of risk of QT prolongation or torsades de pointes. Many medicines have not been tested for this risk in patients, especially those with congenital long QT syndrome.

10.9. Appendix 9: Anticipated Events

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study, the following events will be considered as anticipated events in the target population (adults with RSV infection including those at high risk for RSV-related disease progression and complications):

- Respiratory System
 - Primary viral pneumonia
 - Secondary bacterial pneumonia (including pneumonia attributable to unusual pathogens)
 - Bronchitis or other LRTD leading to hospitalization
 - Other infections (eg, sinusitis, otitis) leading to hospitalization
 - Respiratory failure including acute respiratory distress syndrome
 - Worsening of asthma, asthma attack
 - Exacerbations of COPD
 - Pulmonary edema
 - Pulmonary embolism
 - Lung malignancies
- Cardiovascular/Circulatory System
 - Myocardial infarction
 - Atrial Fibrillation
 - Hypertension
 - Bradycardia
 - Syncope (for other reasons than Torsades de Pointes)
 - Transient ischemic attack
 - Exacerbations of CHF
- Nervous System
 - Stroke
 - Mental status changes
- Digestive System:
 - Liver stasis
 - Colon malignancies
- Urinary System
 - Acute exacerbation of CKD leading to hospitalization
- Endocrine System
 - Decompensation of previously controlled diabetes mellitus leading to hospitalization
- Skeletal System Function
 - Fractures (hip fractures most common)
- Reproductive System
 - Breast malignancies

Reporting of Anticipated Events

These AEs will be captured on the eCRF and in the database, and will be reported to the sponsor as described in Section 8.3 and Appendix 10.4. Any anticipated event that meets SAE criteria will be reported to the sponsor within the appropriate timeline as described in Section 8.3.4. The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

If based on an aggregate review, it is determined that an anticipated event is possibly related to the study intervention, the sponsor will report these events in an expedited manner.

Statistical Analysis

Details of the statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.10. Appendix 10: Pre-Existing Symptom Questionnaire^a

CCI



CCI



10.11. Appendix 11: Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)

CCI



CCI



**10.11.2. Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)
Impact Scales^a**

CCI



CCI



10.12. Appendix 12: Patient Global Impression (PGI-S)**Patient Global Impression of Severityⁱ**

Overall, how severe were your respiratory infection symptoms **today**? (select one)

- ☐ No symptoms today
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

ⁱ(Do not translate) Source: adapted from the FLU-PRO User Manual for RSV.

10.13. Appendix 13: Patient Global Impression of Change (PGI-C)

Adult RSV Patient Global Impression of Change^a

Compared with how you felt before you started taking the study medication, how are your respiratory infection symptoms now? (select one)

- ☐ Much better
- ☐ Somewhat better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Somewhat worse
- ☐ Much worse

^a **Do not translate:** Source: adapted from the FLU-PRO User Manual for RSV infection.

10.14. Appendix 14: Return to Usual Activities**Adult RSV Return to Usual Activitiesⁱ**

Have you returned to your usual activities today? (select one)

- ☐ Yes
- ☐ No

ⁱ(Do not translate) Source: adapted from the FLU-PRO User Manual for RSV infection.

10.15. Appendix 15: Return to Usual Health**Adult RSV Return to Usual Healthⁱ**

Have you returned to your usual health today? (select one)

- ☐ Yes
- ☐ No

ⁱ(Do not translate) Source: adapted from the FLU-PRO User Manual for RSV infection.

10.16. Appendix 16: Employment Status**Employment statusⁱ**

How would you describe your employment status now? (select one)

- ☐ Employed full-time (working at least 30 hours per week)
- ☐ Employed part-time (working less than 30 hours per week)
- ☐ Not currently employed full-time or part-time

Is there anyone who helps you when you are ill who is employed full-time or part-time? (select one)

- ☐ Yes
- ☐ No

ⁱ **(Do not translate)** Source: developed for collection during screening or baseline assessment to determine whether patient will be asked to report hours missed from work in the ePRO during treatment and follow-up for 53718678RSV2008 adult outpatient RSV treatment study in high-risk adults.

10.17. Appendix 17: Hours Missed from Work**Hours missed from workⁱ****Hours missed from Work**

When you are ill with a respiratory infection, sometimes you must take time off from work to recover from your illness or to avoid infecting other people where you work. People who help you when you are ill also may need to take time off from work to do things that you cannot do due to your illness.

What is the **total number of hours of work that you or people who help you missed** due to your respiratory infection **in the past 24 hours**?

_____ total hours missed from workⁱⁱ

Do not translate:

ⁱ For protocol only: Source: question developed for JNJ53718678 RSV2008. Do not include on ePRO application.

ⁱⁱ For ePRO implementation only: use range of 0-100 hours for accepted responses.

10.18. Appendix 18: Clinician Symptom Score**Participant ID :----- Age:----- Visit Day/Date:-----**

Instruction: Based on all the information on an individual participant (history, underlying comorbidity, baseline disease characteristics), overall clinical evaluation as well as interview of the participants on their symptoms, please rate with check mark the presence and severity of the following LRTD sign/symptoms

LRTD Symptom Scoring				
Level	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)
Cough	No Cough	Just noticeable. <i>-Occasional mild, isolated cough</i>	Bothersome sometimes, not interfering with other activities. <i>-Moderate, paroxysmal cough</i>	Bothersome most of the time, interfering with other activities <i>- Severe, strenuous cough, with or without chest discomfort</i>
Sputum production	No sputum	Just noticeable	Bothersome sometimes, not interfering with other activities	Bothersome most of the time, interfering with other activities
Shortness of breath/dyspnea	No episode of shortness of breath or dyspnea	May have brief episodes. <i>Or Breathless while exercise/walking at fast pace, walking uphill</i>	May have increased episodes <i>Or Breathless walking at own pace</i>	May have severe episodes <i>Or Breathless at rest, while talking, changing dress</i>
Wheezing	No wheezing	Terminal expiration or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Rales/Ronchi/Crackles/other lung sounds	No findings of rales/ronchi/crackles	-	Scattered wheeze or ronchi	Widespread wheeze or ronchi, rales, dyspnea or signs of consolidation

10.19. Appendix 19: EQ-5D-5L Questionnaire



Health Questionnaire

English version for the USA

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Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ☐
- I have slight problems walking ☐
- I have moderate problems walking ☐
- I have severe problems walking ☐
- I am unable to walk ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

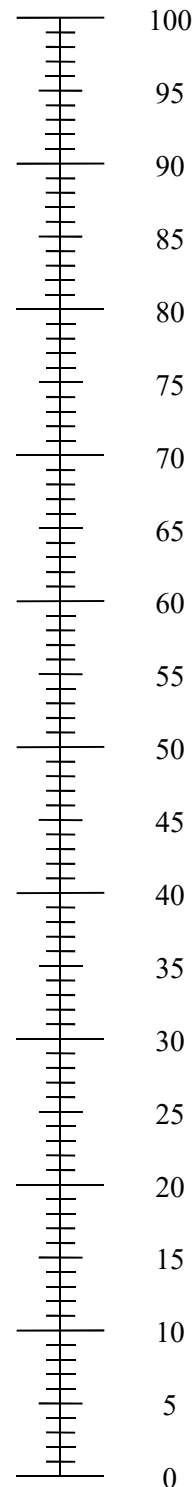
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagineThe worst health
you can imagine

10.20. Appendix 20: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and study site personnel. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the Clinical Study Report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

- These emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19 related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, the original protocol procedures should take preference.
- Virtual visits, missed assessments/visits, and out-of-window visits will be labeled with the prefix "COVID-19-related" in the eCRF/eSource by the site personnel where needed.
- COVID-19 vaccination during study period:

- No change in risk to participant or any interaction with study intervention that could compromise the safety and wellbeing of participants is anticipated.
- As side effects due to vaccination may impact the evaluation of the clinical evolution of RSV symptoms, it is recommended that administration of a COVID-19 vaccine be timed to occur after study completion or at least two weeks after the last dose of study medication. Investigator discretion and overall assessment of clinical stability will be relied on if there is a medical need to administer vaccine during the study period.
- Participant must inform the site if he/she is scheduled to receive an approved COVID-19 vaccine (prophylaxis) during the study period. Documentation of vaccination must be recorded in the participant eCRF.
- Participant Visits/Assessments:
 - In case home visits cannot be performed (either due to institute policy or due to local regulations), such study assessments that can be performed virtually are accepted.
 - There are some assessments that could be conducted virtually via telephone (or other digital options, if possible) with participants' parent(s)/caregiver(s) in their homes. This methodology can only be used in accordance with applicable (including local) laws, regulations, guidelines, and procedures. Please note, the visit windows included in the [Schedule of Activities](#) are still applicable. It must be documented in the eCRF and in the participants' source documents when a visit occurs virtually due to COVID-19.
 - The study assessments that require investigator judgment should be conducted by a qualified site member identified on the site delegation log.
 - If required, nasal mid-turbinate swab can be stored at home and picked up by study site personnel or courier.
 - In case home visits cannot be performed, nasal mid-turbinate swabs, if required as per the [Schedule of Activities](#), may be collected by the participant (or his/her spouse, partner, relative, or other caregiver). Training and written instructions to collect the nasal mid-turbinate swab will be provided to the participant (or his/her spouse, partner, relative, or other caregiver).
- On-site Monitoring Visits:
 - In case on-site monitoring visits are not possible due to local regulations, restrictions and guidance, the Site Manager will conduct site monitoring visits and activities remotely. Additional on-site monitoring visits may be needed in the future to catch up on source data verification. Remote source data verification of

electronic records might be performed if possible and only if allowed by local/national regulations, restrictions, and guidance.

- During the COVID-19 pandemic and at the impacted sites, clinical Site GCP Audits with direct impact/engagement from the clinical investigator team would not be conducted to comply with national, local and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement if possible.
- In all cases, the written main ICF will be obtained prior to any study-specific assessment.

10.21. Appendix 21: Protocol Amendment History

This is an original protocol.

11. REFERENCES

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INVESTIGATOR AGREEMENT

JNJ-53718678 (Rilematovir)

Clinical Protocol 53718678RSV2008

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Janssen Research & Development
PPD _____

Signature: _____ Date: PPD _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S.

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Status: Approved, Date: 12 March 2021

CONFIDENTIAL – FOIA Exemptions Apply in U.S.

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Status: Approved, Date: 12 March 2021