Janssen Research & Development *

Clinical Protocol

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rilematovir in Infants and Children (≥28 Days to ≤5 Years of Age) and Subsequently in Neonates (<28 Days of Age), Hospitalized With Acute Respiratory Tract Infection Due to Respiratory Syncytial Virus (RSV)

Protocol 53718678RSV3001; Phase 3
AMENDMENT 1

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.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	This document
Original Protocol	17 August 2020

Amendment 1 (This document)

Overall Rationale for the Amendment: To add estimand language for the primary endpoint and to revise the assessments for follow-up of participants who prematurely discontinued the study intervention/the study. Additional modifications and clarifications have been added.

Section Number and Name	Description of Change	Brief Rationale
1.3.1 During Hospitalization 1.3.2 After Discharge	Specifics were added on the monitoring of ObsRO Signs/Symptoms and ObsRO GHQ completion	Clarification
1.3.1 During Hospitalization	Additional blood pressure assessment on Day 1 was removed in the Schedule of Activities During Hospitalization	Blood pressure assessment on Day 1 was corrected while maintaining the bid assessment on that day
1.3.1 During Hospitalization	Reference to footnote d was removed for Day 14 in the Schedule of Activities During Hospitalization	No sample for clinical laboratory assessments is collected on Day 14
1.3.2 After Discharge	The concomitant medication review on Day 35 was updated from optional to mandatory assessment in the Schedule of Activities After Discharge	Review of the concomitant medication is mandatory until the end of the study
5.1 Inclusion Criteria	Inclusion Criterion 1 was made more specific	To clarify that correction for gestational age will only be applied for participants who were born preterm
1.1 Synopsis 4.1 Overall Design 5.1 Inclusion Criteria	Inclusion Criterion 5 was updated	To ensure enrollment of participants with at least moderate RSV disease severity who are more likely to potentially benefit from RSV treatment
1.1 Synopsis 6.1 Study Intervention(s) Administered	The dilution step for the preparation of the suspension for dosing in neonates was removed	Dosing accuracy studies confirmed the neonate starting dose can be administered with the 1 mL oral syringe using the 20 mg/mL strength of the suspension
6.8 Concomitant Therapy	The use of mucolytics was recommended to be limited	To be limited to use in line with the clinical practice guidelines and package inserts
6.8 Concomitant Therapy 10.19 Appendix 19: Guidance on Study Conduct during the COVID-19 Pandemic	Specifics were added on the administration of a locally approved (including emergency use-authorized) COVID-19 vaccine	Additions were made per recent Health Authority guidance
1.3 Schedule of Activities 6.3 Measures to Minimize Bias: Randomization and Blinding	Continuation of the study assessments and visits, including the Day 35 Follow-up visit, as per the Schedule of	Additions were made to allow completion of all study visit assessments also for

Section Number and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention 7.3 Lost to Follow-up	Activities, till the end of study was added as preferred option for all participants who early discontinue study intervention	participants who prematurely discontinue study intervention
1.3 Schedule of Activities 7.2 Participant Discontinuation/Withdrawal From the Study	A safety follow-up visit in case of withdrawal of consent for study participation was added	To maximize safety follow-up
8.1.1.1 RSV Recovery Scale Assessments	The protocol-defined RRS categories were further specified	Clarifications
4.1 Overall Design 8.1.1.3 ClinRO and ObsRO Clinical Outcome Assessments and Caregiver Impact Questions	• Timing for completion of the PRESORS assessments in bid schedule was specified • Additional instructions for clinicians and parents/caregivers were added with regards to the rating of each RSV sign/symptom in the PRESORS ClinRO and ObsRO assessments • Wording was added to emphasize the value of the Caregiver Impact Questions	Clarifications
8.3.5.1 Hepatobiliary Effects	"ALT elevation" was replaced by "Hepatobiliary effects" as safety topic of special interest	Alignment with the Investigator's Brochure
1.1 Synopsis 8.3.5.1 Hepatobiliary Effects 9.4.3 Safety Analyses 10.2 Appendix 2: Clinical Laboratory Tests 10.4.3 Severity Criteria 10.6 Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1; July 2017)	Additional laboratory assessments were included as reflex testing	For further evaluation of the origin of the elevation of potential hepatobiliary enzymes
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting 8.3.5.2 RSV-related Complications	Information on RSV-related complications was moved to Section 8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	RSV complications are not considered a safety topic of special interest per the Investigator's Brochure
1.1 Synopsis 9.4.2.1 Primary Endpoint	"At a minimum" was removed and "RRS category at baseline" was added when defining the variables to be included for the proportional odds model	Based on Health Authority request to specify the primary analysis unambiguously
9.4.2.1.1 Estimand	Estimand attributes for the primary endpoint were added	Addition as requested by Health Authority
10.5 Appendix 5: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007, draft)	Laboratory toxicity range for Grade 2 hypernatremia and Grade 2 hematuria were revised	Correction
10.7 Appendix 7: Cardiovascular Safety – Abnormalities	Appendix 7: values for vital signs abnormalities for age group 3 to ≤5 years were updated	To implement values for this age group per recent literature

Section Number and Name	Description of Change	Brief Rationale
10.10 Appendix 10: Parent/Caregiver Information v9 (04 May 2021) 10.11 Appendix 11: Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS) v9 Caregiver Diary (ObsRO PRESORS, 04 May 2021)	• Appendix 10 was split in 2 appendices (ie, Appendix 10 and Appendix 11) affecting the numbering of all subsequent appendices • Minor changes were made	Clarification
10.12 Appendix 12: Caregiver Impact Questions v9 (04 May 2021)	Minor changes were made, including renumbering of the questions	Per requirements from the eCOA smartphone and web diary applications that will be used in this study; correction of typographical errors, clarification of instructions
10.13 Appendix 13: Clinician PRESORS v9 (04 May 2021)	• Question 15 was removed • Minor changes were made	Readiness for discharge/medical need for hospitalization will be captured in the eCRF
10.14 Appendix 14: Definitions of Resolved/Not Resolved Based on the ObsRO Signs/Symptoms 10.15 Appendix 15: Definitions of Resolved/Not Resolved Based on the ClinRO Signs/Symptoms	Wording adjustments were made	To align with the wording in the PRESORS version used in the current study
10.19 Appendix 19: Guidance on Study Conduct during the COVID-19 Pandemic	• Wording was added to specify the clinical management of laboratory confirmed SARS-CoV-2 infection in study participants, ie, per local standard-of-care • Section for "Study conduct related to COVID-19 vaccine deployment for non-COVID-19 clinical trials" was added	Clarification
1.1 Synopsis 2.2 Background 3 OBJECTIVES AND ENDPOINTS 8.1.1.2 Other Clinical Course and Clinical Severity Assessments	"medical need for" ICU was changed to "requiring" ICU	For consistency with wording in the RRS definitions
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rilematovir in Infants and Children (≥28 Days to ≤5 Years of Age) and Subsequently in Neonates (<28 Days of Age), Hospitalized With Acute Respiratory Tract Infection Due to Respiratory Syncytial Virus (RSV).

Note: The substudy at specific sites will be initiated only after positive recommendation by the Independent Data Monitoring Committee (IDMC) upon review of interim analysis 1 results of the main study. "Subsequently in neonates" refers to the main study being opened for enrollment of neonates at all sites following completion of a prior substudy in neonates, IDMC review of the substudy data, and positive recommendation. This protocol only describes the main study. The specifics to the substudy will be described in a separate substudy protocol.

Rilematovir is an investigational, potent small-molecule RSV-specific fusion inhibitor belonging to the indole chemical class. Rilematovir targets the RSV 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	
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the clinical outcome on the RSV Recovery Scale (RRS).	• RRS[a] as assessed on the first study day when at least 50% of the participants across treatment arms are discharged from the hospital (the study day for the RRS evaluation will be determined based on blinded data at the first interim analysis by an independent statistician).
Secondary	
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to clinical resolution of RSV disease.	• Proportion of participants clinically resolved from RSV disease based on Clinician Reported Outcome (ClinRO) Signs/Symptoms[c,e] as assessed on the same study day as the primary endpoint.
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the time from first dosing to resolution of Key RSV Signs/Symptoms[b] including supplementation free.	• Time from first study dose to resolution of Key RSV Signs/Symptoms (absent or mild)[d,e] based on parent's/caregiver's Observer Reported Outcome (ObsRO) Signs/Symptoms and supplementation free (oxygen and feeding/hydration) for at least 24 hours.
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the time from discharge to resolution of Key RSV Signs/Symptoms.	• Time from discharge to resolution of Key RSV Signs/Symptoms[d,e] based on ObsRO Signs/Symptoms (only including participants who did not reach resolution before first discharge).
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the time	• Time from first dosing to end of oxygen supplementation (only including participants who were receiving oxygen supplementation at the time of first dosing).

Objectives	Endpoints
from first dosing to end of oxygen supplementation.	
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the incidence of post-baseline RSV-related complications.	• Incidence in post-baseline RSV-related complications.
• To evaluate the safety and tolerability of rilematovir.	• Safety and tolerability, as assessed by adverse events (AEs), clinical laboratory testing, electrocardiograms (ECGs), vital signs throughout the study.
• To evaluate the effect of rilematovir on the clinical course of RSV disease as assessed electronically by ObsRO Signs/Symptoms and ObsRO General Health Questions (GHQ).	• The following endpoints will be based on the ObsRO Signs/Symptoms: ♦ time to resolution of signs/symptoms (absent or mild)[e] of RSV disease; ♦ actual values and changes from baseline in scores. • The following endpoint will be based on the ObsRO GHQ: ♦ time to improvement.
• To evaluate the effect of rilematovir on the clinical course of RSV disease as assessed electronically by ClinRO Signs/Symptoms and ClinRO GHQ.	• The following endpoints will be based on the ClinRO Signs/Symptoms: ♦ time to resolution of signs/symptoms (absent or mild)[e] of RSV disease; ♦ actual values and changes from baseline in scores; ♦ proportion of participants clinically resolved from RSV disease based on ClinRO Signs/Symptoms[c,e] as assessed each day from Day 2 to 8. • The following endpoint will be based on the ClinRO GHQ: ♦ general impression of change.
• To evaluate the effect of rilematovir on the clinical course of RSV disease (other than ClinRO and ObsRO assessments).	• RRS[a] as assessed each day separately from Days 2 to 8. • Time to hospital discharge from start of dosing. • Time to readiness for hospital discharge. • Proportion of participants requiring intensive care unit (ICU) stay. • Duration of requiring ICU stay. • Proportion of participants requiring rehospitalization for respiratory/other reasons. • Proportion of participants requiring oxygen supplementation.

Objectives	Endpoints
	• Duration of oxygen supplementation. • Time to end of supplemental feeding/hydration. • Proportion of participants requiring hydration and/or feeding by intravenous (IV) administration or nasogastric tube. • Duration of supplemental feeding/hydration. • Time to end of supplementation (oxygen and/or feeding/hydration). • Number and type of medical encounters. • Incidence of antibiotic treatment episodes. • Incidence of systemic or inhaled corticosteroids and bronchodilators use.
• To evaluate the antiviral effect of rilematovir as measured by RSV viral load in nasal mid-turbinate (MT) swab samples by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay.	• RSV viral load (area under the RSV viral load-time curve [AUC]) from immediately prior to first dose of study intervention (baseline) through Day 3, Day 5, and Day 8. • RSV viral load and change from baseline over time. • Proportion of participants with undetectable RSV viral load at each time point of assessment throughout the study.
• To evaluate the emergence of mutations in the viral genome potentially associated with resistance to rilematovir.	• Sequence changes (post-baseline) in the RSV F gene compared to baseline.
• To evaluate the pharmacokinetics (PK) of rilematovir.	• PK parameters of rilematovir.
• To explore the PK/pharmacodynamic (PD) relationships of rilematovir for efficacy and safety.	• PK/PD analysis of PK of rilematovir and selected primary and secondary efficacy and safety parameters.
• To evaluate the acceptability and palatability of the rilematovir formulation.	• Acceptability and palatability of the rilematovir formulation as assessed through a questionnaire.
Exploratory	
• To explore other effects of rilematovir on the clinical course of RSV disease.	• Time from first dosing to peripheral capillary oxygen saturation (SpO_2) ≥92% on room air among participants who were not on oxygen supplementation prior to the onset of respiratory signs/symptoms. • Respiratory rate, heart/pulse rate, body temperature, and SpO_2 over time as measured by the investigator (during scheduled visits).

Objectives	Endpoints
	• Proportion of participants with signs/symptoms of RSV disease at discharge according to last ClinRO Signs/Symptoms evaluation prior to discharge. • The ClinRO Signs/Symptoms score for each sign/symptom according to last evaluation prior to discharge in those participants not resolved at discharge.
• To explore the effect of rilematovir on the impact of the child's RSV disease on the parent(s)/caregiver(s) and family based on the PRESORS Caregiver Impact Questions.	• Extent of the parent's/caregiver's worry about the child's health. • Time missed from usual activities by the parent/caregiver. • Time missed from work by anyone in child's household due to the child's illness.
• To explore the relationship between antiviral activity and the primary and key secondary clinical outcomes.	• RSV viral load based endpoints and primary and key secondary clinical course endpoints.
• To explore the evaluation of biomarkers associated with RSV or treatment effects (optional).	• Specific biomarkers in leftover blood samples and nasal MT swabs (optional).

a. For details on the RRS see Section 8.1.1.1.
b. Signs are defined as objective evidence of the disease, which are apparent to the physician during examination (such as tachycardia, tachypnea, chest wall retractions, grunting, and nasal flaring). Symptoms are defined as subjective manifestations of the diseases, reported by the participant or by the parent(s)/caregiver(s), but not necessarily apparent to the physician during examination (such as rhinorrhea, cough, feeding difficulties, disturbed sleep, and disturbed activity level). Throughout this protocol, the notation "signs/symptoms" is used.
c. Clinical resolution is defined by: free of oxygen supplementation, AND free of supplemental feeding, AND not requiring ICU, AND Key RSV Signs/Symptoms resolved to absent or mild as per the ClinRO Signs/Symptoms (see also Section 8.1.1.2).[e]
d. Key RSV Signs/Symptoms are: Breathing problems, retractions, tachypnea, cough, wheezing (ClinRO Signs/Symptoms only), breathing sounds (ObsRO Signs/Symptoms only), and tachycardia (see also Section 8.1.1.3).
e. See Section 10.14, Appendix 14 and Section 10.15, Appendix 15 for definitions of resolved/not resolved.
f. See Section 8.1.1.2 for the list of complications assessed.

Hypothesis

The primary hypothesis of this study is that treatment with rilematovir improves clinical outcome of RSV infection as compared to placebo in hospitalized pediatric participants as assessed with the RRS on the first study day when at least 50% of the participants across treatment arms are discharged from the hospital.

OVERALL DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, interventional study in infants and children (≥28 days to ≤5 years of age) and subsequently in neonates (<28 days of age), hospitalized (refers to having planned at least 24 hours with an overnight stay in the hospital) with RSV infection. The substudy at specific sites will be initiated only after positive recommendation by the IDMC upon review of interim analysis 1 results of the main study. "Subsequently in neonates" refers to the main study being opened for enrollment of neonates at all sites following completion of a prior substudy in neonates, IDMC review of the substudy data, and positive recommendation. This protocol only describes the main study. The specifics to the substudy will be described in a separate substudy protocol.

Study participants with signs/symptoms of an acute respiratory illness supporting a diagnosis of RSV infection (see Table: RSV Disease Signs/Symptoms for Eligibility) will be identified and tested for RSV infection when they are hospitalized or present to the ER/clinic and are expected to be hospitalized. Participants should only be screened if they are expected to be randomized within ≤3 days of RSV sign/symptom onset.

Participants with RSV disease (ie, at least 1 sign/symptom of upper respiratory tract infection [URTI], at least 1 sign/symptom of lower respiratory tract infection [LRTI], and at least 1 systemic/general sign/symptom [see Table: RSV Disease Signs/Symptoms for Eligibility]) will be enrolled. Cough or wheezing cannot be the only LRTI sign/symptom present, ie, at least one other LRTI sign/symptom needs to be present for eligibility. Eligible participants can be otherwise healthy or have (a) risk factor(s) for severe RSV disease (as defined in the Table: Risk Factors for Severe RSV Disease). Those who are immunocompromised and those with neuromuscular diseases that affect swallowing or the thoracic muscles are excluded from participation.

Table: RSV Disease Signs/Symptoms for Eligibility

Upper Respiratory Tract Infection (URTI) Signs/Symptoms:
Nasal congestion
Rhinorrhea
Lower Respiratory Tract Infection (LRTI) Signs/Symptoms:
Increased respiratory efforts, evidenced by:
– subcostal, intercostal, or tracheosternal retractions
– grunting
– head bobbing
– nasal flaring
– tachypnea
Wheezing[a]
Cyanosis
Cough[a]
Apnea
Systemic / General Signs/Symptoms:
Feeding difficulties (defined as <75% intake of normal food amounts)
Dehydration
Fever
Disturbed sleep
Disturbed activity level (irritable, restless, agitated, or less responsive)

[a] Cough or wheezing cannot be the only LRTI sign/symptom present, ie, at least one other LRTI sign/symptom needs to be present for eligibility.

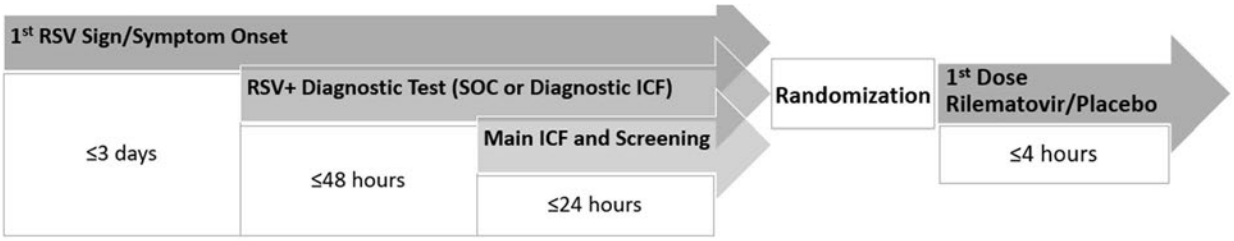
Table: Risk Factors for Severe RSV Disease

Prematurity at birth[a]
Bronchopulmonary dysplasia
Congenital heart disease
Down syndrome
Neuromuscular impairment[b]
Cystic fibrosis
Recurrent wheezing[c]
Asthma
Other congenital disease

[a] ***Note:*** Prematurely born participants are only eligible for this study if their age corrected for gestational age at birth is ≥28 days at the time of consent.[1] After this main study opens to neonate enrollment: prematurity is not allowed for neonates (ie, neonate participants should have been born at term, after at least 37 weeks of gestation).
[b] Excluding neuromuscular diseases that affect swallowing or the thoracic muscles.
[c] Recurrent wheezing is defined as ≥1 episode of wheezing without a cold in the past year.[22]

Participants will be randomized in a 2:1 ratio to receive either rilematovir or placebo bid. Randomization should occur within a maximum of 24 hours after start of screening or within 48 hours after collection of the standard-of-care (SOC) sample used for local RSV diagnosis, whichever comes first, and no later than 3 days after RSV sign/symptom onset (see Figure: Timeline from RSV Sign/Symptom Onset to First Dose). Randomization will be stratified by presence of risk factors for severe RSV disease (presence of [a] risk factor[s] for severe RSV disease vs otherwise healthy, see Table: Risk Factors for Severe RSV Disease) and by region (Asia-Oceania, EMEA, Northern America, and Latin America-The Caribbean).

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



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

Study intervention administration should start as soon as possible, but no later than 4 hours after randomization. Dosing will be based on a mg/kg basis per age group and 4 age groups are defined based on the participant's age at the time of consent:

- Age group 1: ≥28 days to <3 months of age (ie, 28 to 91 days of age, extremes included);
- Age group 2: ≥3 months to <6 months of age (ie, 92 to 182 days of age, extremes included);
- Age group 3: ≥6 months to ≤5 years of age (ie, 183 to 1,826 days, extremes included);
- Age group 4*: at term birth (ie, after at least 37 weeks of gestation) to <28 days of age (ie, 1 day to 27 days, extremes included).

*After opening of recruitment in neonates in the main study dependent on positive IDMC recommendation after completion of a substudy in neonates.

An IDMC will be commissioned for this study.

The end of study is considered as the last visit (phone visit or on-site visit) for the last participant in the study.

NUMBER OF PARTICIPANTS

A sample size of approximately 737 hospitalized RSV-infected participants is targeted.

INTERVENTION GROUPS AND DURATION

The study will include a Screening Period (Day -1 to Day 1), a Treatment Period (Day 1 to Day 8), and a Follow-up Period (Day 9 to Day 35 [±3]). The total study duration for each participant will be approximately 36 days (Screening included).

Eligible participants will be randomized 2:1 (active:placebo) to receive either rilematovir or placebo bid for 7 days (14 consecutive doses). For participants who receive only 1 dose of rilematovir or placebo PM of Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all participants receive 14 consecutive doses in total.

Treatment Overview

Treatment	Age Group	Age Range	Dosing Regimen[a]	Volume Oral Suspension[b]
Rilematovir	1	≥28 days to <3 months	2.5 mg/kg bid on Days 1 to 7(/8)	A mL
	2	≥3 to <6 months	3 mg/kg bid on Days 1 to 7(/8)	B mL
	3	≥6 months to ≤5 years	4.5 mg/kg bid on Days 1 to 7(/8)	C mL
	4*	birth at term to <28 days	X[c] mg/kg bid on Days 1 to 7(/8)	D[c] mL
Placebo	1,2,3, or 4*	see above	Matching placebo bid on Days 1 to 7(/8)	A, B, C, or D[c]* (respectively) mL placebo

bid = twice daily; IDMC = Independent Data Monitoring Committee; IWRS = interactive web response system.
* After opening of recruitment in neonates in the main study dependent on positive IDMC recommendation after completion of a substudy in neonates.

a. Doses are provided for JNJ-53718678-AAA.

b. A to D represents the volume of oral rilematovir suspension to obtain the required dose of JNJ-53718678-AAA or the volume of the matching placebo suspension. After reconstitution, rilematovir is dosed as an equivalent 20 mg/mL JNJ-53718678-AAA oral suspension (containing 23 mg/mL JNJ-53718678-ZCL, the hemi-tartrate of JNJ-53718678-AAA), to be used depending on the bodyweight of the participant. The required volume to be administered per intake will be calculated by the IWRS and provided to the sites.

c. Dose dependent on outcome of the substudy in neonates and following IDMC review and recommendation. The dosing regimen will not exceed the exposures simulated for the bid regimen in pediatric subjects ≥28 days to ≤5 years of age and observed for the 250 mg bid regimen in adults.

Description of Interventions

Study supplies will be delivered as a powder and solvent for oral suspension, to be reconstituted by appropriately trained study site personnel prior to administration/dispensing to the participant's parent(s)/caregiver(s). The study intervention is administered orally using a dosing syringe and is administered regardless of food intake. During hospitalization the study intervention may also be administered through nasogastric tube, if already in place.

EFFICACY EVALUATIONS

RSV Recovery Scale Assessments

The RRS is an ordinal scale assessing a participant's clinical status as defined per protocol. The study day on which the RRS will be assessed as the primary endpoint is the first study day when at least 50% of the participants across treatment arms are discharged from the hospital (with or without signs/symptoms). This study day will be determined in a blinded manner based on all available data irrespective of the treatment

group at the time of the first interim analysis and by an independent statistician in order to protect data integrity. This study day will be used for any further interim analysis as well as for the final analysis. The RRS will also be assessed on Days 2 to 8 (excluding the primary time point) as secondary endpoints.

The RRS provides 7 mutually exclusive conditions ordered from best to worst, and the analysis score reflects the participant's worst situation on the study day of assessment:

1. Not Hospitalized Without Signs/Symptoms*

2. Not Hospitalized With Signs/Symptoms*

3. Non-ICU Hospitalization, Not Requiring Supplemental Oxygen NOR Supplemental Feeding/Hydration

4. Non-ICU Hospitalization, Requiring Supplemental Oxygen AND/OR Supplemental Feeding/Hydration

5. Admitted to the ICU, Not Requiring Mechanical Ventilation**

6. Requiring Mechanical Ventilation**

7. Death

*With or without signs/symptoms is defined by the Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms assessment as being not resolved or resolved (absent or mild), respectively (see Section 10.14, Appendix 14).
**Mechanical ventilation includes both invasive and non-invasive mechanical ventilation.

Other Clinical Course and Clinical Severity Assessments

The study will include the following additional evaluations of the clinical course of RSV disease:

- Clinical resolution from RSV disease as assessed daily from Day 2 to Day 8, and defined by:
  - Free of oxygen supplementation, AND
  - Free of supplemental feeding, AND
  - Not requiring ICU, AND
  - Key RSV Signs/Symptoms resolved to absent or mild as per the ClinRO Signs/Symptoms.
- Evolution and severity of signs/symptoms of RSV disease as assessed by the parent(s)/caregiver(s) (ObsRO Signs/Symptoms) and by the investigator (ClinRO Signs/Symptoms) on an electronic device.
- Evolution of the RSV disease based on ObsRO GHQ and ClinRO GHQ as assessed by the parent(s)/caregiver(s) and by the investigator, respectively, on an electronic device.
- Oxygen supplementation requirement type (invasive mechanical, non-invasive mechanical, and non-invasive non-mechanical), and duration.
- Hydration and feeding by IV line/nasogastric tube and duration.
- The occurrence of the following RSV-disease related complications, with onset after treatment initiation, as reported by the investigator as AE based on the available clinical information:
  - Respiratory complications: respiratory failure, apnoeic attacks, bronchiolitis/bronchial obstruction, pneumonia, asthmatic crisis;
  - Infectious complications: otitis media, bacterial respiratory tract infections, sepsis;

- Cardiovascular complications: arrhythmia, cardiogenic shock, hemodynamic instability, congestive cardiac failure;
- Acid-base or electrolyte complications, based on laboratory values if considered clinically relevant:
  - metabolic acidosis (serum HCO_3^- <16),
  - metabolic alkalosis (serum HCO_3^- >30);
  - hyponatremia (Na^+ <130 mEq/L),
  - hypokalemia (K^+ <2.9 mEq/L),
  - hyperkalemia (K^+ >6.0 mEq/L),
  - hypocalcemia (Ca^{2+} <7.7 mg/dL or equivalent to Grade 2 in children ≤3 months),
  - hypercalcemia (Ca^{2+} >11.9 mg/dL or equivalent to Grade 2 in children ≤3 months),
  - hypoglycemia (glucose <54 mg/dL)
  - hyperglycemia (glucose >160 mg/dL).

- Clinical parameters: respiratory rate, heart/pulse rate, SpO_2, and body temperature as measured by the investigator during scheduled visits.
- Time to first hospital discharge (from start of dosing).
- Time to readiness for hospital discharge.
- Reason for hospital discharge or for no discharge despite being clinically ready for discharge.
- The requirement for transition to ICU and duration of ICU stay.
- Proportion of participants requiring rehospitalization for respiratory/other reasons.
- Number and type of medical encounters.
- Incidence of antibiotic treatment episodes.
- Incidence of systemic or inhaled corticosteroids and bronchodilators use.
- Impact of child's RSV disease on the parent(s)/caregiver(s) and family as assessed by the Caregiver Impact Questions.

Antiviral Activity

The RSV viral load in nasal MT swab samples 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. Nasal MT swab specimens for the determination of RSV viral load will be collected at several timepoints during the study as indicated in the Schedule of Activities. The RSV viral load data from the baseline predose nasal MT swab will also be used for central confirmation of the local RSV diagnosis. Date and time of sampling will be collected. Nasal MT swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). The nostril that was sampled will be documented by the study site personnel.

Viral Sequencing

Viral resistance will be monitored by sequencing of the RSV F gene in all baseline (predose or screening) nasal MT swab samples and in subsequent samples upon request of the sponsor's virologist. Other regions

of the RSV genome may also be sequenced at discretion of the sponsor's virologist. Sequencing results will 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.

PHARMACOKINETIC EVALUATIONS

PK assessments during the study will be based on sparse sampling to limit the number of samples (2 samples, see Section 1.3.3, Pharmacokinetic Assessments Sampling Schedule) and will be analyzed using a population (pop)PK model.

OTHERS

Pharmacokinetics/Pharmacodynamics

Obtained PK and PD data (selected antiviral activity parameters, clinical outcomes, and safety parameters) will be used to explore the relationship between the PK and PD.

Medical Encounters

Medical encounters will be collected in the electronic case report form (eCRF) for all participants from time of presentation at the hospital/clinic throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses.

Acceptability and Palatability

Acceptability and palatability of the rilematovir formulation will be assessed using a questionnaire completed by parent(s)/caregiver(s) on an electronic device after last dosing.

Biomarkers

No specific samples will be collected for biomarker research. Leftover blood samples and leftover nasal MT swab samples collected during the study may be used for exploratory biomarker analyses (eg, proteins, ribonucleic acid [RNA], immune cells, microbiome) at the sponsor's discretion and results may be reported separately from this study.

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 nasal MT swab sample collected at baseline by PCR assay at the central laboratory. Central testing for other respiratory viruses will also include testing for the presence of SARS-CoV-2 in the nasal MT swab sample. Nasal MT swabs from other time points may also be assessed for detection of other respiratory viruses or bacteria at the central laboratory, if deemed necessary.

SAFETY EVALUATIONS

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

AEs, serious (S)AEs, and deaths;

Clinical laboratory tests (central);

ECG 12-lead (central);

Vital signs (resting, in supine position):

- vital signs assessments performed as part of the clinical course of RSV infection-related assessments (body temperature, heart/pulse rate, respiratory rate, and SpO_2),
- additional vital signs assessments: systolic blood pressure (SBP), diastolic blood pressure (DBP);

Complete physical examination of all body systems performed at Screening (including height or length, head circumference, and body weight measurements), and directed physical examinations performed, inclusive of the examination needed for ClinRO Signs/Symptoms completion, as per the Schedule of Activities (on Day 21, including height or length, head circumference, and body weight measurements). Clinically relevant findings resulting from the physical examination post-baseline will be reported as AEs, except those in the ClinRO Signs/Symptoms assessment that are treated as efficacy outcomes.

In the event that an invasive procedure such as a blood draw or nasal swab and an ECG are required at approximately the same time, the ECG should be collected first.

Safety and tolerability will be evaluated throughout the study from signing of the main informed consent form (ICF) until the last study-related activity. For participants with only a signed pre-screening (diagnostic) ICF (ie, for whom consent was not given to enroll in the main study), only study procedure (nasal swabbing) related AEs will be reported.

STATISTICAL METHODS

Sample Size Calculation

The study will aim to enroll 737 participants. The sample size calculation is based on the primary endpoint, ie, the RRS and results from Study 53718678RSV2002. Based on the proportional odds model and assuming a benefit of approximately 45% reduction of the common odds ratio, a total sample size of 700 participants (randomized 2:1) would provide a power of at least 95%, using an overall Type 1 error rate of 5% (2-sided) and accounting for the group-sequential design. A reduction of 35%, which is still considered clinically relevant, would provide a power of 80%. Assuming 5% of participants will be excluded from the primary analysis set (intent to treat – infected [ITT-i] set), the total sample size for this study is 737.

In the sample size calculation, it is assumed that the distribution of participants treated with placebo between the categories of the RRS will be as follows on the selected study day:

- Not hospitalized without signs/symptoms: 20%
- Not hospitalized with signs/symptoms: 20%
- Non-ICU hospitalization, not requiring supplemental oxygen nor supplemental feeding/hydration: 15%
- Non-ICU hospitalization, requiring supplemental oxygen and/or supplemental feeding/hydration: 30%
- Admitted to the ICU, not requiring mechanical ventilation: 7%
- Requiring mechanical ventilation: 7%
- Death: 1%

Efficacy Analysis

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, a hierarchical testing procedure will be applied to control for the overall Type I error rate at the 5% level (2-sided). The following endpoints are included in the confirmatory testing strategy:

1. RRS, ie, the primary endpoint.
2. Proportion of participants clinically resolved from RSV disease (based on ClinRO Signs/Symptoms as assessed at the same study day as the primary endpoint).
3. Time from first dosing to resolution of Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms and supplementation-free for at least 24 hours.
4. Time from discharge to resolution of Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms (for participants who did not reach resolution before first discharge).
5. Time from first dosing to end of oxygen supplementation (for participants who were receiving oxygen supplementation at the time of first dosing).
6. Incidence in post-baseline RSV-related complications.

Primary Endpoint

The primary efficacy analysis will be based on the ITT-i analysis set and consists of the analysis of the RRS.

A proportional odds model will be used to analyze the RRS, including treatment, RRS category at baseline, and the two stratification factors (stratification by presence of [a] risk factor[s] for severe RSV disease versus otherwise healthy and by region).

Key Secondary Endpoints

For the hypothesis testing, the following methods will be used:

- Time from first dosing to resolution of Key RSV Signs/Symptoms (based on ObsRO Signs/Symptoms), time from discharge to resolution of Key RSV Signs/Symptoms (based on ObsRO Signs/Symptoms), and time from first dosing to end of oxygen supplementation will be analyzed using a stratified Gehan-Wilcoxon test (using the randomization stratification factors).
- To compare the proportion of participants clinically resolved from RSV (based on ClinRO Signs/Symptoms), a logistic regression model will be used. Randomization stratification factors will be added to the model. A similar model will be applied to analyze the incidence of treatment-emergent RSV-related complications.

Clinical Course of RSV Infection

Endpoints related to evaluation of the clinical course of RSV infection will be analyzed graphically and descriptively as described in the statistical analysis plan (SAP). 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. Time to-variables will be analyzed using Kaplan-Meier (KM) plots and will be modeled using an accelerated failure time model, adjusted for the randomization stratification factors, to estimate differences between intervention groups.

Antiviral Activity

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

Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood-based repeated measures approach. 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 95% 2-sided confidence intervals.

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 or any worsening of a pre-existing condition occurring at or after the initial administration of study intervention through the end of the study is considered to be treatment-emergent (TEAE). All reported TEAEs will be included in the analysis. For each TEAE, 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 and markedly abnormal results 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 or with any markedly abnormal laboratory results will be provided.

The laboratory abnormalities will be graded per the criteria specified in the Division of Microbiology and Infectious Diseases (DMID) pediatric toxicity tables and in accordance with the normal ranges of the clinical laboratory if no DMID gradings were available. Alkaline phosphatase (ALP) will be graded per the criteria specified in the Division of Acquired Immunodeficiency Syndrome (DAIDS) adult and pediatric toxicity table. For breast feeding neonates, total bilirubin will also be graded per the DAIDS adult and pediatric toxicity table.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations and pre- versus 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

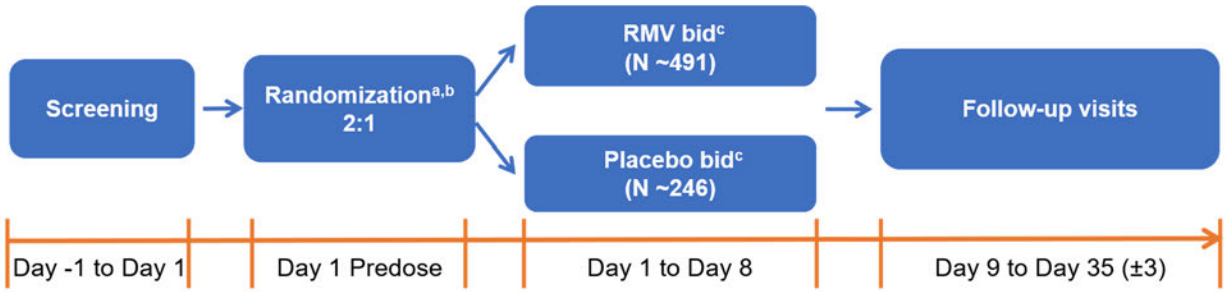
Descriptive statistics of actual values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Interim Analyses

Two interim analyses are planned. Each interim analysis will preferably be conducted at the end of a Northern or Southern hemisphere RSV season. The first interim analysis will be performed at the end of the first season where the cumulative enrollment reaches approximately 35% of the total sample size and will include an assessment of futility. The second interim analysis will be performed at the end of the first season where the cumulative enrollment reaches approximately 75% of the total sample size and will include an assessment of futility and stopping for early superiority. At the second interim analysis, proper alpha correction will be applied using the O'Brien Fleming alpha spending function to correct for multiplicity. An additional interim analysis with assessment of stopping for early superiority might be performed at the end of an RSV season after the second pre-planned interim analysis, provided that approximately 85% of the total sample size is enrolled. In case an additional interim analysis is performed, proper alpha correction will be applied using the O'Brien Fleming alpha spending function.

1.2. Schema

Figure 1: Schematic Overview of the Study



bid = twice daily; RMV = rilematovir; RSV = respiratory syncytial virus; SOC = standard-of-care.

a) Randomization should occur within a maximum of 24 hours after start of screening or within 48 hours after collection of the SOC or pre-screening samples for RSV diagnosis, whichever comes first. A study participant should be randomized ≤3 days after RSV sign/symptom onset.

b) Randomization will be stratified by the presence of risk factors for severe RSV disease and by region.

c) 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 bid for 7 days (14 consecutive doses).

1.3. Schedule of Activities

1.3.1. During Hospitalization

During Hospitalization													
Phase	**Screening[a]**	**Predose[a]**	**Treatment Phase**					**Follow-up[b]**					
Day	**-1 to 1**	**1**	**2[c]**	**3**	**4-7**	**8 (+1)[d]**		**9-13**	**14 (±1)**	**15-20**	**21 (±3)[d]**	**22-34**	**35 (±3) End-of-study**
Study Procedures													
Screening/Administrative													
Pre-screening (diagnostic) ICF (optional)[e]	X												
Informed Consent (ICF)	X												
Eligibility criteria[f]	X												
Participant characteristics and demographics	X												
Medical history/prior medications/medical encounters from presentation to hospital/clinic up to screening	X												
Record clinical assessments performed at presentation to hospital/clinic prior to hospitalization/ enrollment (based on source documents)[g]	X												

During Hospitalization													
Phase	**Screening[a]**	**Predose[a]**	**Treatment Phase**					**Follow-up[b]**					
Day	**-1 to 1**	**1**		**2[c]**	**3**	**4-7**	**8 (+1)[d]**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)[d]**	**22-34**	**35 (±3) End-of-study**
Record presence of Key RSV Signs/Symptoms at presentation to hospital/clinic prior to hospitalization/ enrollment (based on source documents)[h]	X												
Local RSV diagnosis in nasal MT swab or SOC sample[i]	X												
Nasal MT swab: RSV viral load and viral sequencing (central)[i]	X												
Randomization		X[j]											
Study Intervention Administration													
Dosing study intervention[k,l]			X[l]/ bid[l]	bid	bid	bid	(X)[l]						
Provision of study intervention for daily use at home at discharge[m]				(X)	(X)	(X)							
Efficacy Assessments													
Clinical evaluation[n]	X	X[x]	X[r]	bid	bid	bid	bid	bid	bid	X	X		(X)[y]
Oxygen and feeding supplementation and hospitalization status[o]	Continuously												
ClinRO Signs/Symptoms[p]	X	X[x]	X[r]	bid	bid	bid	bid	X	X	X	X		
ClinRO GHQ[p]	X	X[x]	X[r]	bid	bid	bid	bid	X	X	X	X		
ObsRO Signs/Symptoms[q]	X	X[x]	X[r]	bid	bid	bid	bid	bid	bid	X	X[s]		
ObsRO GHQ[q]	X	X[x]	X[r]	bid	bid	bid	bid	bid	bid	X	X[s]		

During Hospitalization													
Phase	**Screening[a]**	**Predose[a]**	**Treatment Phase**					**Follow-up[b]**					
Day	**-1 to 1**	**1**		**2[c]**	**3**	**4-7**	**8 (+1)[d]**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)[d]**	**22-34**	**35 (±3) End-of-study**
Caregiver Impact Questions[q]	X	X[x]	X[r]	X	X	X	X	X	X	X	X[s]		
Site Study Personnel to monitor the timely and accurate completion of ObsRO Signs/Symptoms and ObsRO GHQ[t]	Continuously												
Nasal MT swab for RSV diagnosis confirmation, RSV viral load, presence of other respiratory viruses and/or bacteria, viral sequencing (central)[w]		X[u]											
Nasal MT swab for RSV viral load and viral sequencing (central)[v,w]				X	X	X	X		X		X		
Medical encounters	Continuously												
Safety Assessments													
Systolic and diastolic blood pressure[z]	X	X[x]	X	bid	bid	bid	bid	bid	bid	X	X		(X)[y]
Complete physical examination (all body systems)[aa]	X												
Directed physical examination[bb]							X		X		X[cc]		(X)[y]
ECG (12-lead)[dd]	X		X[ee]		X[ee]		X				X		(X)[y]
Clinical Laboratory Assessments													
Blood sampling for hematology and biochemistry[ff]	X[gg]						X[gg]				X		(X)[y]

During Hospitalization													
Phase	**Screening[a]**	**Predose[a]**	**Treatment Phase**					**Follow-up[b]**					
Day	**-1 to 1**	**1**		**2[c]**	**3**	**4-7**	**8 (+1)[d]**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)[d]**	**22-34**	**35 (±3) End-of-study**
Urinalysis[hh]	X						X				X		(X)[y]
Pharmacokinetics (see Section 1.3.3 for Schedule)													
PK samples			X[ii]	X[ii]									
Acceptability/Palatability													
Acceptability/ palatability questionnaire[q] for parent(s)/caregiver(s)							X						
Ongoing Participant Review													
Adverse events	Continuously												
Concomitant medication	Continuously												

a. Screening/predose assessments can begin after main ICF signature and must finish prior to first study intervention intake. These assessments and eligibility confirmation are permitted to continue into the next calendar day, but then randomization and first study intervention intake will promptly follow and this date is considered Day 1.

b. If a participant prematurely discontinues study intervention for any reason, the parent(s)/caregiver(s) will be asked to complete the visits (with the participant) and all assessments per the SOA (until visit Day 35). If a participant prematurely discontinues the study intervention, and the parent(s)/caregiver(s) are not willing to complete the regular SOA, the parent(s)/caregiver(s) will be asked to return with the participant to the site for Withdrawal and Follow-up visits. These visits should preferably occur 1 day and 14 days after the last study intervention intake and include the same assessments as the Day 8 and Day 21 visits, respectively, and the follow-up visit Day 35 with its assessments. In case the participant prematurely discontinues study participation, a Safety Follow-up Visit will be offered, which will include the same safety assessments as on Day 21.

c. The investigator will use his/her clinical judgment to discharge a participant on or after Day 2, following completion of the required investigator-performed assessments for that day, with exception of PM bid assessments.

d. Window applies only to clinical laboratory assessments (blood sampling for hematology and biochemistry, and urinalysis).

e. The participant's legally acceptable representative may initially sign a pre-screening (diagnostic) ICF to allow collection and testing of a nasal MT swab for the purpose of study eligibility. This does not apply if diagnostic sampling is SOC and yields a positive RSV result. The main ICF must be signed within 24 hours of the pre-screening or SOC sample collection.

f. The investigator will ensure each participant meets all study eligibility criteria prior to randomization. The investigator should withdraw a participant whose clinical status changes (eg, receipt of additional laboratory results or medical records) before first study intervention intake in case (s)he no longer meets all eligibility criteria.

g. Includes same items as the clinical evaluation and complete physical examination performed at screening, as available.

h. Key RSV Signs/Symptoms are: Breathing problems, retractions, tachypnea, wheezing, cough, and tachycardia.

i. Study site personnel will diagnose RSV locally for eligibility, using a study-specific nasal MT swab and a PCR or other molecular-based diagnostic assay. They should ship the leftover specimen for any patient that is subsequently randomized. This does not apply if an SOC diagnostic sample is collected within 24 hours of screening start and yields a positive RSV result using a molecular-based diagnostic assay.
j. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC or pre-screening sample used for local RSV diagnosis, whichever comes first AND within ≤3 days of RSV sign/symptom onset (see Figure 2).
k. First study intervention intake signifies Day 1 and should occur as soon as possible, but no later than 4 hours after randomization. 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 participant will receive study intervention orally using a dosing syringe, or a nasogastric tube if one is already in place, and with or without food.
l. Depending on the time of randomization/enrollment, participants 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 PM of Day 1, dosing continues through the morning (ie, AM) of Day 8 so that all participants receive 14 doses in total.
m. Study site personnel will instruct the participants' parents/caregivers on how to store and administer the study intervention at home. They will provide the study intervention bottle(s) at discharge, from which the parent/caregiver should withdraw each dose remaining in the treatment period.
n. Clinical evaluation includes vital signs assessments: respiratory rate, heart/pulse rate, body temperature, and SpO_2. Study site personnel should measure body temperature immediately before or >4 hours after a participant receives an antipyretic. Study site personnel should interrupt supplemental oxygen until the SpO_2 drops below 92% and remains stable at that level for 1 minute, or up to 15 minutes, whichever comes first before measuring SpO_2, unless the participant is on invasive or non-invasive mechanical ventilation. Refer to Section 10.9, Appendix 9 for guidelines for measuring vital signs and SpO_2.
o. Supplemental oxygen requirement (type and duration), supplemental feeding (type and duration), level of and duration of hospital care, and duration of hospitalization are recorded throughout the study. Duration requires start and end dates/times.
p. The investigator will complete the ClinRO Signs/Symptoms and ClinRO GHQ on an electronic device. In case of a missing assessment, the reason should be documented in the eCRF.
q. Participant's parent(s)/caregiver(s) will complete the assessments on an electronic device. The study site personnel will explain to participant's parent(s)/caregiver(s) how to use the electronic device and when to complete assessments.
r. The clinical evaluation, ClinRO Signs/Symptoms, ClinRO GHQ, ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions assessments on Day 1 need to be completed after the PM administration of the study intervention.
s. The participant's parent(s)/caregiver(s) should complete the final ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions before attending or as the first activity of the Day 21 visit. The last assessment should be completed on calendar day 21 in case the Day 21 visit takes place after calendar day 21.
t. In case of a missing assessment, the reason should be documented in the eCRF.
u. Study site personnel should collect the pre-dose nasal MT swab as close as possible and prior to first study intervention intake. 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 whole remainder of the original sample is available).
v. Study site personnel should collect each nasal MT swab from the same nostril (unless precluded due to bleeding) and most preferably at approximately the same time as on Day 1. Figure 3 summarizes the nasal MT swab collection schedule.
w. The sponsor may utilize leftover nasal MT swab samples for exploratory biomarker analyses.
x. Only performed if the screening assessment occurred >8 hours before anticipated first dosing.
y. Only applicable if clinically indicated to evaluate a participant's ongoing AE(s) or any clinically significant laboratory or ECG abnormality identified on Day 21.
z. Refer to Section 10.9, Appendix 9 for guidelines for measuring vital signs. Efficacy assessments require other vital signs (footnote n).
aa. Complete physical examination of all body systems includes measurement of height or length, head circumference, and body weight.
bb. Directed physical examination includes respiratory system, nose, ear, throat, facial and neck lymph nodes.

cc. On Day 21, also includes measurement of height or length, head circumference, and body weight.
dd. Study site personnel should perform each 12-lead ECG prior to other scheduled assessments. The participant should be supine (infants can be lying on their parent's/caregiver's arm) and rested for at least 5 minutes and preferably sleeping or calm (ie, not crying). The investigator should repeat an ECG in the presence of an abnormal QTcF interval (see Sections 5.2, 7.1, and 8.3.5.2), or for other ECG abnormalities at his/her discretion. A central cardiologist will also evaluate all ECGs, but not in real time (within 72 hours).
ee. Study site personnel should take the Day 1 and Day 3 ECGs approximately one hour (45-90 minutes) after administration of study intervention.
ff. A central laboratory analyzes the hematology and biochemistry samples. Participants may begin study intervention before the central laboratory delivers screening results.
gg. Levels of potassium and magnesium will be determined by the central laboratory. In case of hypokalemia and/or hypomagnesemia at screening or at Day 8, the levels of potassium and/or magnesium should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at local laboratory) may be required.
hh. The central laboratory provides urine dipsticks for local assessment. Study site personnel should ship any specimen with an abnormality to the central laboratory for flow cytometric and/or microscopic evaluation(s).
ii. Refer to Section 1.3.3 Pharmacokinetic Assessments Sampling Schedule for collection timepoints.

Notes:

1. Unscheduled visits may be performed based on the investigator's clinical judgment and may include further evaluations, as needed.
2. See Section 10.19, Appendix 19 for guidance on study conduct during the 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.

1.3.2. After Discharge

After Discharge[a]												
Phase	**Treatment Phase**						**Follow-up[b]**					
Day	**2**	**3**	**4**	**5 (±1)**	**6-7**	**8 (+1)[c]**	**9-13**	**14 (±1)[c]**	**15-20**	**21 (±3)[c]**	**22-34**	**35 (±3) End-of-study**
		On-site visit[d]		**On-site visit[d]**		**On-site visit[d]**		**On-site visit[d]**		**On-site visit[d]**		**Phone follow-up/ Conditional[e] On-site visit[d]**
Study Procedures												
Study Intervention Administration												
Dosing study intervention[f,g]	(X)	bid	bid	bid	bid	(X)[g]						
Efficacy Assessments												
Clinical evaluation[h]		X		X		X		X		X		(X)[i]
ClinRO Signs/Symptoms[j]		X		X		X		X		X		
ClinRO GHQ[j]		X		X		X		X		X		
ObsRO Signs/Symptoms[l]	bid[k]	bid	bid	bid	bid	bid	bid	bid	X	X[m]		
ObsRO GHQ[l]	bid[k]	bid	bid	bid	bid	bid	bid	bid	X	X[m]		
Caregiver Impact Questions[l]	X	X	X	X	X	X	X	X	X	X[m]		
Site study personnel to monitor the timely and accurate completion of ObsRO Signs/Symptoms and ObsRO GHQ[n,o]	Continuously											
Nasal MT swab for RSV viral load and viral sequencing (central)[p,q]		X		X		X		X		X		
Medical encounters	Continuously											
Safety Assessments												
Systolic and diastolic blood pressure[r]		X		X		X		X		X		(X)[i]
Directed physical examination[s]						X		X		X[t]		(X)[i]

After Discharge[a]												
Phase	**Treatment Phase**						**Follow-up[b]**					
Day	**2**	**3**	**4**	**5 (±1)**	**6-7**	**8 (+1)[c]**	**9-13**	**14 (±1)[c]**	**15-20**	**21 (±3)[c]**	**22-34**	**35 (±3) End-of-study**
		On-site visit[d]		**On-site visit[d]**		**On-site visit[d]**		**On-site visit[d]**		**On-site visit[d]**		**Phone follow-up/ Conditional[e] On-site visit[d]**
ECG (12-lead)[u]		X[v]				X				X		(X)[i]
Clinical Laboratory Assessments												
Blood sampling for hematology and biochemistry[w]						X[x]				X		(X)[i]
Urinalysis[y]						X				X		(X)[i]
Acceptability/Palatability												
Acceptability/palatability questionnaire for parent(s)/caregiver(s)						X						
Ongoing Participant Review												
Adverse events	Continuously											
Concomitant medication	Continuously											

a. In case a participant is re-hospitalized prior to Day 8, the investigator should make every effort to record the reason for rehospitalization and perform all assessments per the Hospitalization SOA, if practically feasible.
b. If a participant prematurely discontinues study intervention for any reason, the parent(s)/caregiver(s) will be asked to complete the visits (with the participant) and all assessments per the SOA (until visit Day 35). If a participant prematurely discontinues the study intervention, and the parent(s)/caregiver(s) are not willing to complete the regular SOA, the parent(s)/caregiver(s) will be asked to return with the participant to the site for Withdrawal and Follow-up visits. These visits should preferably occur 1 day and 14 days after the last study intervention intake and include the same assessments as the Day 8 and Day 21 visits, respectively, and the follow-up visit Day 35 with its assessments. In case the participant prematurely discontinues study participation, a Safety Follow-up Visit will be offered, which will include the same safety assessments as on Day 21.
c. Window applies to all assessments of the on-site visit (or home visit, if applicable, see footnote d).
d. On-site visits are preferred; a study site may perform home visits if feasible and local regulations allow.
e. Study site personnel should follow up with the participant's parent(s)/caregiver(s) by telephone. The investigator will review the participant's ongoing AE(s) or any clinically significant laboratory or ECG abnormality identified on Day 21, and use his/her clinical judgment to schedule a physical visit and any clinically relevant assessments.
f. Dosing should occur approximately every 12 hours. The participant will receive study intervention orally using a dosing syringe and with or without food.
g. For participants who received only 1 dose of study intervention PM of Day 1, dosing continues through the morning (ie, AM) of Day 8 so that all participants receive 14 doses in total.

h. Clinical evaluation includes vital signs assessments: respiratory rate, heart/pulse rate, body temperature, and SpO_2. Study site personnel should measure body temperature immediately before or >4 hours after a participant receives an antipyretic. Study site personnel should interrupt supplemental oxygen until the SpO_2 drops below 92% and remains stable at that level for 1 minute, or up to 15 minutes, whichever comes first before measuring SpO_2. Refer to Section 10.9, Appendix 9 for guidelines for measuring vital signs and SpO_2.
i. Only applicable in case of on-site visit and if clinically relevant.
j. The investigator will complete the ClinRO Signs/Symptoms and ClinRO GHQ on an electronic device. In case of a missing assessment, the reason should be documented in the eCRF.
k. A parent/caregiver should complete the morning ObsRO Signs/Symptoms and ObsRO GHQ prior to discharge.
l. Parent(s)/caregiver(s) will complete the ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions at home after discharge.
m. The participant's parent(s)/caregiver(s) should complete the final ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions before attending or as the first activity of the Day 21 visit. The last assessment should be completed on calendar day 21 in case the Day 21 visit takes place after calendar day 21.
n. At least the responses to the ObsRO GHQ should be reviewed by the study site personnel. In case of significant deterioration of the child's health, the study site personnel should contact the parent(s)/caregiver(s) by phone (or other means of contact as agreed upon).
o. In case of a missing assessment, the reason should be documented in the eCRF.
p. Study site personnel should collect each nasal MT swab from the same nostril (unless precluded due to bleeding) and most preferably at approximately the same time as on Day 1. Figure 3 summarizes the nasal MT swab collection schedule.
q. The sponsor may utilize leftover nasal MT swab samples for exploratory biomarker analyses.
r. Refer to Section 10.9, Appendix 9 for guidelines for measuring vital signs. Efficacy assessments require other vital signs (footnote h).
s. Directed physical examination includes respiratory system, nose, ear, throat, facial and neck lymph nodes.
t. On Day 21, also includes measurement of height or length, head circumference, and body weight.
u. Study site personnel should perform each 12-lead ECG prior to other scheduled assessments. The participant should be supine (infants can be lying on their parent's/caregiver's arm) and rested for at least 5 minutes and preferably sleeping or calm (ie, not crying). The investigator should repeat an ECG in the presence of an abnormal QTcF interval (see Sections 7.1, and 8.3.5.2), or for other ECG abnormalities at his/her discretion. A central cardiologist will also evaluate all ECGs, but not in real time (within 72 hours).
v. Study site personnel should take the Day 3 ECG approximately one hour (45-90 minutes) after administration of study intervention.
w. A central laboratory analyzes the hematology and biochemistry samples.
x. Levels of potassium and magnesium will be determined by the central laboratory. In case of hypokalemia and/or hypomagnesemia at Day 8, the levels of potassium and/or magnesium should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at local laboratory) may be required.
y. The central laboratory provides urine dipsticks for local assessment. Study site personnel should ship any specimen with an abnormality to the central laboratory for flow cytometric and/or microscopic evaluation(s).

Notes:

1. Unscheduled visits may be performed based on the investigator's clinical judgment and may include further evaluations, as needed.
2. See Section 10.19, Appendix 19 for guidance on study conduct during the 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.

1.3.3. Pharmacokinetic Assessments Sampling Schedule

		Day 1			Day 2			
		Post-dose AM	**Pre-dose PM**	**Post-dose PM**	**Pre-dose AM**	**Post-dose AM**	**Pre-dose PM**	**Post-dose PM**
First Dose AM	**Option 1**	X			Y			
	Option 2*	X					Y	
First Dose PM	**Option 1**			X	Y			
	Option 2*			X			Y	

X: The C_{max} PK sample will be taken after the first dose intake, after the ECG measurement (see Schedule 1.3.1) and approximately 1 hour (45-120 minutes) after dosing.
Y: The C_{trough} PK sample will be taken between 4 hours post-dose and 30 minutes pre-dose. To allow for flexibility with taking this sample, 2 different time points are given as options.
*Option 2 should be considered only if the Day 2 sample can be collected prior to discharge.

Blood samples for determination of rilematovir concentrations will be collected through finger prick or heel stick. Leftover blood samples collected for PK assessments may be used for exploratory biomarker analyses, at discretion of the sponsor. The following times need to be recorded: date and time of last study intervention intake, date and time of PK blood sampling, and time of any meal consumed within 30 minutes before or after the previous study intervention intake.

2. INTRODUCTION

Respiratory syncytial virus (RSV), a negative-stranded ribonucleic acid (RNA) virus belonging to the *Pneumoviridae* family, is considered the most important cause of acute lower respiratory tract infection (LRTI) in infants and young children.[20,37] Two subtypes of RSV have been identified, ie, subtypes A and B that generally co-circulate simultaneously.[16] 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.[2,4,44]

In most patients, RSV results in upper respiratory tract infection (URTI) eliciting "common cold"-like symptoms, which might last up to 2 weeks, and are usually self-limiting. However, hospitalizations occur, with hospitalizations in the United States for RSV estimated at 55.3/100,000 person-years between 1993 and 2008 for all ages.[45] RSV infection can result in LRTI/lower respiratory tract complications (LRTC) with severe respiratory compromise, causing considerable morbidity and mortality in certain patient populations, such as infants.[37]

RSV-related LRTI is a major cause of hospital admissions and death in young children worldwide.[36,37] Infants born prematurely or close to the RSV season and/or suffering from bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe RSV-related acute LRTI.[17] In 33-35 week gestational age infants, the incidence rate of hospitalization for RSV ranged from 3.25% to 3.63%, with hospitalization rates peaking from December-March in the northern hemisphere.[3] In 2015, there were approximately 33.1 million RSV-LRTI episodes in children up to 4 years of age globally, which resulted in approximately 3.2 million hospitalizations and 59,600 deaths for this age group. Approximately 45% of these hospital admissions and in-hospital deaths occurred in children younger than 6 months of age.[37] Among children <5 years of age with RSV infection, 97.7% present for medical care as outpatients in emergency departments (EDs) and in pediatric practices, while 2.7% require hospitalization.[19]

In children ≤3 years of age, the clinical presentation of RSV disease is linked to the anatomy of their maturing respiratory tract. RSV infection causes inflammation and necrosis of the bronchiolar epithelial cells. The lumina of the bronchioles become obstructed from edema of the airway wall, increased mucus secretion, sloughed epithelium, and cellular debris. The small-diameter airways in infants are particularly vulnerable to obstruction. Such obstruction of bronchioli may lead to bronchiolitis and can cause respiratory distress.[30,31] Between 61.3% and 77.5% of acute bronchiolitis episodes in children <2 years have been reported as being RSV-related.[12] Hence, this population is considered at risk for severe RSV-related disease.

The duration and level of distress and anxiety of the parent/caregiver due to severe RSV infection are underestimated.[29] Bronchiolitis symptoms usually peak around Day 3 to Day 5 and in case of early presentation (Day 2), the clinical course may deteriorate before improving.

In immunocompetent children and adults, a 3-day window between the onset of clinical symptoms after RSV infection and peak viral load has been reported, which provides an effective window of opportunity to initiate treatment.[10,11,14] Additionally, some studies in the adult and pediatric population have demonstrated that RSV viral load and severity of disease symptoms are closely

correlated.[10,11,14] Together, these data suggest that early initiation of treatment after RSV infection is possible, and could result in a decrease of the viral load, syncytia formation, and in inflammatory reactions,[14] and hence may improve disease outcomes and shorten the duration and/or severity of the disease.

Despite the large medical and economic burden, no vaccines and only 2 antiviral agents have been approved for the prevention or treatment of RSV infection in pediatric populations, while no vaccine or antiviral has been approved for adults.[2,6,35] Palivizumab, a monoclonal antibody, is only approved for prophylaxis of RSV infection with restricted indication for infants at risk of severe RSV disease. However, its prophylactic effectiveness is limited (55% reduction in hospitalization rate), and it has not proven to be an effective treatment option.[38] Ribavirin (aerosol), a nucleoside analogue, is approved in selected countries for the treatment of hospitalized infants and children with severe LRTI, but is not recommended for use per guidelines[28] and its use is minimal due to limited efficacy, potential genotoxic effects, and complexity of administration.[2,5,39] In hospitalized patients, the current treatment of RSV infection is generally limited to supportive care, consisting of supplemental oxygen therapy, nutrition, fluids, and, in some cases, mechanical ventilation.[15,40] Overall, the unmet medical need (prophylactically and therapeutically) is substantial in both children and adults with RSV infection, whether hospitalized or outpatients.

For the most comprehensive nonclinical and clinical information regarding rilematovir, refer to the latest version of the Investigator's Brochure (IB).[26] The term “study intervention” throughout the protocol refers to the administration of rilematovir or placebo.

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.

2.1. Study Rationale

RSV is considered one of the most important viruses causing acute LRTI and a major cause of hospital admissions and death in young children worldwide.[36,37] Infants born prematurely or at the beginning of the RSV season and/or suffering from bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe RSV-related acute LRTI.[17]

Besides ribavirin and palivizumab with their respective associated limitations as described above, there is no direct-acting antiviral agent approved for the prevention or treatment of RSV infection in the pediatric population. Also, no vaccines have been approved to prevent RSV infection. Therefore, a substantial medical need for the treatment of RSV infection exists.

This study aims to evaluate the efficacy and safety of rilematovir in hospitalized infants and children (≥28 days to ≤5 years) and, subsequent to the completion of the substudy, in hospitalized neonates (born at term, <28 days of age) with RSV infection.

2.2. Background

For the most comprehensive nonclinical and clinical information regarding rilematovir, refer to the latest version of the IB for rilematovir.[26]

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.[8,27] Rilematovir is an investigational RSV specific fusion inhibitor belonging to the indole chemical class and is in development for the treatment of RSV infection. Rilematovir has demonstrated in vitro activity against a panel of RSV-A and RSV-B strains. 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 infected with RSV (interim analysis Study 53718678RSV2004), and in RSV-infected hospitalized pediatric participants (Study 53718678RSV1005 and interim analysis Study 53718678RSV2002).

Nonclinical Studies

Rilematovir has been extensively evaluated and characterized in both in vitro and in vivo pharmacological and toxicological studies. Detailed results of nonclinical studies are described in the IB for rilematovir.[26]

Rilematovir is a small molecule inhibitor of the RSV fusion protein with demonstrated activity against RSV in in vitro and in vivo models of RSV infection. No in vitro antiviral activity was observed for the rilematovir metabolites M12 (JNJ-53541683), M19 (JNJ-64564071), and M37 (JNJ-69101045); the effective concentration for 50% inhibition (EC_{50}) value for M5 (JNJ-54172794) was 7.7 nM.

In vitro, rilematovir is a moderate to strong inhibitor of cytochrome P450 (CYP)3A4/5, an inducer of CYP3A4 and, to a lesser extent, of CYP2B6. Rilematovir is a substrate, but not an inhibitor, of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and an inhibitor of organic-anion-transporting polypeptide (OATP)1A2, OATP1B1, OAT3, organic cation transport (OCT)1, and OCT2.

In the in vitro human-ether-a-gogo-related (hERG) assay, rilematovir induced changes but this did not translate to QT interval corrected for heart rate (QTc) interval prolongation in animals. In dogs, an increase in heart rate and decrease in blood pressure were observed. Minimally and transiently decreased neuromuscular function, with minimal effects related to gastrointestinal function were observed in rats. Decreased general activity and tremors (minipig only) were reported in adult dogs and minipigs given high doses of rilematovir and were considered secondary to the poor general condition of the animals.

Repeated-dose toxicity studies up to 4 weeks of dosing in adult rats, dogs, and minipigs identified the liver and gastrointestinal system as target systems. Administration of rilematovir in juvenile rats up to the maximum feasible dose of 400 mg/kg/day was generally well tolerated and no target organs of toxicity were identified. In juvenile minipigs, dose levels of 25 mg/kg/day and above resulted in gastric ulceration and inflammation, decreases in red blood cells with increases in bilirubin, and adaptive changes in hematopoietic organs (extramedullary hematopoiesis in liver and spleen). There were no toxicologically relevant effects on embryo-fetal development in pregnant rats and rabbits, while maternal toxicity was evident.

No genotoxic or phototoxic effects have been identified for rilematovir. Rilematovir is not irritating to the eye or skin sensitizing. The compound was classified as moderately cytotoxic in a high content screen assay, it did not induce mitochondrial toxicity.

In conclusion, the results of the safety pharmacology, genetic toxicology, and general toxicity studies in adult and juvenile animals and embryo-fetal development studies support the administration of rilematovir to humans (adult and pediatric population).

Clinical Studies

Human Pharmacokinetics and Product Metabolism

Single Dose

In the single-dose escalation part of Study 53718678RSV1001 in healthy adults, 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 area under the plasma concentration-time curve (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 1.00 hour, except for the 1,000-mg dose group, in which it was 2.50 hours. Similar mean apparent terminal elimination half-lives ($t_{1/2term}$) 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 are similar between Caucasian and Japanese participants.

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 supratherapeutic 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 ΔΔQTcI (90% 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 msec (4.2; 5.3 msec) and 20.3 msec (18.2; 22.3 msec), respectively. The highest C_{max} at the effect compartment following a single dose associated with an upper limit of the 90% CI for ΔΔQTcI <10 msec was 4,350 ng/mL, which corresponds with approximately a single dose of 1,000 mg. For more details on the analysis, refer to the IB.[26] A change to a twice daily (bid) dosing regimen (see Section 4.3) and several other mitigation measures to safeguard the participants (see Section 2.3.3) have been implemented.

Multiple Dose

Adult Population

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 bid regimen compared with the 500 mg once daily (qd) regimen. For the 500 mg q24h dose group, mean plasma concentration 24 h after time of administration (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 q12h dose group, mean C_{12h}, C_{max} and $AUC_{0\ 12h}$ 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 pharmacokinetic (PK) profile of rilematovir at multiple doses of 75 mg, 200 mg, and 500 mg qd 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.

Interim analysis results from Study 53718678RSV2004 in RSV-infected adult patients (data cut-off 23 September 2019) demonstrate that the population (pop)PK model provides an adequate description of most of the data, however moderate variability existed with exposures greater (~25%) than expected based on healthy volunteer data. The mean (standard deviation [SD]) Day 7 AUC_{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).

Pediatric Population

An initial popPK model for rilematovir has been developed using data from Study 53718678RSV1001 in healthy adults and data from Study 53718678RSV1005 in RSV-infected pediatric patients. The popPK model has a combination of maturation functions as well as allometric scaling, taking into account the abundancy of specific enzymes (and their maturation) involved in the metabolism of rilematovir in the different age groups. Using this popPK model, the rilematovir PK parameters $AUC_{0\ 24h}$, C_{min}, and C_{max} were simulated for the pediatric population for Days 1 and 7 in Study 53718678RSV1005. At the highest doses of 5, 6, and 9 mg/kg qd for the respective age groups, the predicted $AUC_{0\ 24h}$, C_{min}, and C_{max} values were similar or slightly higher than the corresponding PK parameters observed for 500 mg rilematovir qd in healthy adults.

The popPK model for rilematovir was updated based on additional adult data (from selected Phase 1 Studies 53718678RSV1007, 53718678RSV1009, and 53718678RSV1008 as well as Phase 2 Study 53718678RSV2004) and pediatric data of Phase 2 Study 53718678RSV2002. Interim analysis results from the ongoing Study 53718678RSV2002 in RSV-infected pediatric patients (data cut-off 02 January 2020) demonstrate that the updated popPK model provides an adequate description of the majority of the data. The observed medians, 5^{th} and 95^{th} percentiles, are in agreement with the simulated prediction intervals. The observed exposures at steady state AUC_{24h} Day 7 across the age groups is in agreement with the 500 mg once daily data in adults and slightly lower than the PK results from Study 53718678RSV1005.

Food Interaction

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

The interim PK results from Study 53718678RSV1007 Part 6, which is at the final analysis stage, demonstrated similar bioavailability of the oral suspension reconstituted from powder and solvent (formulation to be used for this study) compared to the oral solution formulation, 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.

Metabolite Profile

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 $AUC_{0\ 96h}$ 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. The most important fecal metabolites were primary oxidative metabolites, and in urine, a multitude of minor metabolites were present. The overall comparison of duodenal fluid and feces profiles demonstrated almost complete conversion of the glucuronides to their aglycon; there was overall a good qualitative and quantitative correlation between both profiles.

When the abundance of rilematovir and its metabolites was determined in plasma of healthy volunteers in Study 53718678RSV1001, similar results were obtained: Rilematovir was the main

circulating entity; M12 represented more than 10% of total drug related material (TDRM), and M37 represented 9.79%.

Drug-Drug Interaction

In clinical Study 53718678RSV1002, coadministration of rilematovir and a drug cocktail consisting of CYP enzyme probe drugs (for CYP3A4, CYP1A2, and CYP2C9) and a non-selective P-gp substrate (fexofenadine) suggested that, after single- and multiple-dose administration, rilematovir is a weak inhibitor and a weak inducer of CYP3A4. 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.

In clinical Study 53718678RSV1006, rilematovir was coadministered with itraconazole (a strong CYP3A4 and P-gp inhibitor) and with rifampicin (an inducer of CYP3A4, glucuronyl transferase [UGT], and P-gp, and an inhibitor of OATP). $AUC_{0\infty}$ of rilematovir increased approximately 3-fold upon coadministration with itraconazole 200 mg qd. 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 qd decreased the exposure of rilematovir, primarily due to induction of CYP3A4.

Efficacy

Adult Population

In the challenge Study 53718678RSV2001 in healthy adult participants inoculated with RSV-A Memphis 37b virus, mean and median RSV viral load AUC from baseline until discharge were lower for all rilematovir dosing groups (75 mg qd, 200 mg qd, or 500 mg qd rilematovir for 7 days) as compared to the placebo group, with a large variability observed in each of the rilematovir dosing groups as well as in the placebo group. No clear dose-response relationship was observed. This was paralleled with lower clinical symptom scores and mucus production for the rilematovir dosing groups as compared to the placebo group. Hence, antiviral proof-of-concept for rilematovir has been established.

In the interim analysis (data cut-off 23 September 2019, N 67) of pilot Phase 2a Study 53718678RSV2004 in adult non-hospitalized RSV-infected participants, 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. From Day 2 through Day 8, however, 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 placebo. 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 6 days in the rilematovir 500 mg group, 8 days in the rilematovir 80 mg group, and 8 days in the placebo group. A similar trend was observed in the subgroup of participants with ≤3 days from symptom onset. Data from this study showed a favorable trend on the time to resolution of Key RSV Signs/Symptoms in the rilematovir treatment groups as compared to placebo, especially in the subgroup of participants with ≤3 days since symptom onset.

Pediatric Population

Study 53718678RSV1005

In Study 53718678RSV1005 in pediatric participants hospitalized due to RSV infection, a trend towards an early antiviral effect of rilematovir was observed, despite a limited data set particularly in the placebo arm. An effect on viral load change from baseline on Days 2 and 3, of 1 to 2 logs difference compared to placebo was observed, as well as an effect on viral load AUC from baseline through Days 3 and 7 (20 to 25% reduction compared to placebo). The exploration of the effects on the clinical course of RSV infection did not reveal a difference between participants who had received rilematovir and those who had received placebo in this limited dataset. No dose-response relationship was observed across the rilematovir dose levels.

Study 53718678RSV2002

In the interim analysis (data cut-off 02 January 2020) of the ongoing Study 53718678RSV2002 in pediatric participants hospitalized (Cohort 1) and non-hospitalized (Cohort 2) with RSV infection, 149 participants were evaluable for efficacy analysis (111 participants in Cohort 1 and 38 participants in Cohort 2). In Cohorts 1 and 2 combined, in Cohort 1, and in the subgroup of participants with ≤3 days since symptom onset, a trend towards a favorable antiviral effect of rilematovir was observed for both the rilematovir low dose and the high dose groups compared to placebo.

In Cohort 1 (hospitalized participants), the mean nasal RSV viral load AUC through Day 5 was lower for the rilematovir low dose and high dose groups than for placebo, with a difference (95% CI) versus placebo of -1.46 (-3.360; 0.449) and -1.60 (-3.494; 0.288) $\log_{10}$ copies.day/mL, respectively. For the subgroup of participants with ≤3 days since symptom onset, the difference in mean viral load AUC through Day 5 for the rilematovir low dose and high dose groups versus placebo was -3.22 (-6.106; -0.327) and -1.82 (-4.758; 1.109) $\log_{10}$ copies.day/mL, respectively.

In Cohort 1 and in the subgroup of participants with ≤3 days since symptom onset, a greater mean change from baseline in nasal RSV viral load was observed for the rilematovir low dose and high dose groups than for placebo.

In Cohort 1, the median (95% CI) time to first confirmed undetectable nasal RSV viral load based on KM analysis was 10.9 (7.05; 12.90) days and 7.8 (6.00; 9.83) days in the rilematovir low dose

and high dose groups, respectively, compared to 13.8 (8.99; 17.73) days in the placebo group. In the subgroup of participants with ≤3 days since symptom onset, the median time to first confirmed undetectable nasal RSV viral load was 12.7 (8.50; 13.88) days and 9.4 (6.65; 18.97) days in the rilematovir low dose and high dose groups, respectively, compared to 13.4 (7.74; 13.95) days in the placebo group.

Conclusions on the clinical course endpoints are given for Cohort 1 and for the subgroup of participants with ≤3 days since symptom onset. In Cohort 1, a clinically relevant benefit was observed for several clinical course endpoints and this benefit was greater in the subgroup of participants with ≤3 days since symptom onset, supporting further study of that subgroup in the Phase 3 studies.

- Mean (SD) decreases in Overall RSV severity score based on Pediatric RSV Electronic Severity and Outcome Rating Systems (PRESORS) Observer Reported Outcome (ObsRO) Signs/Symptoms were greater in the rilematovir high dose group as of Day 3 through Day 21 compared to the rilematovir low dose and the placebo groups. A similar pattern was present in the ≤3 days since symptom onset subgroup. The same was observed for the Key RSV Signs/Symptoms score.

- The median (95% CI) KM time to resolution of all RSV signs/symptoms based on ObsRO Signs/Symptoms was shorter in the rilematovir low and high dose groups compared to placebo (6.00 [4.29; 9.18], 6.85 [5.29; 10.79] and 8.32 [6.74; 10.85] days, respectively). Similarly, this was observed for the Key RSV Signs/Symptoms (4.63 [3.94; 6.86] and 6.31 [3.92; 8.37] days in the rilematovir low and high dose treatment groups and 7.91 [5.15; 9.92] days in the placebo group) and in the ≤3 days since symptom onset subgroup (6.63 [2.12; 9.70 and 4.93 [3.80; 9.81] versus 9.29 [6.93; 12.18]).

- No relevant differences in time to hospital discharge between treatment groups were observed in Cohort 1. In the subgroup with symptom onset ≤3 days, KM median (95% CI) time to hospital discharge was approximately 3 days and 1 day shorter in the rilematovir high dose and low dose groups (3.77 [2.00; 7.67] and 5.69 [2.95; 6.03] days, respectively) compared to the placebo group (6.79 [1.97; 7.11] days).

- No relevant differences in time to investigator-defined clinical stability between treatment groups were observed in Cohort 1, whereas for the subgroup with symptom onset ≤3 days, there was approximately 1 day difference between the rilematovir high dose group and the placebo group (4.46 [2.97; 6.75] days, 3.96 [1.83; 7.86] days for the rilematovir low and high dose groups versus 5.09 [2.95; 7.81] for the placebo group).

- The median (95% CI) time to end of supplemental oxygen based on KM analysis in Cohort 1 was 2.49 (1.47; 4.91) days and 2.65 (1.54; 3.95) days in the rilematovir low dose and high dose groups, respectively, compared to 2.57 (0.90; 3.16) days in the placebo group. In the subgroup with symptom onset ≤3 days, that time was approximately 1 day shorter in the rilematovir high dose group as compared to placebo (3.61 [1.69; 5.63] days

and 2.80 [1.21; 5.65] days in the rilematovir low dose and high dose groups, respectively, versus 3.79 [1.40; 7.62] days in the placebo group).

- The median time to peripheral capillary oxygen saturation (SpO_2) ≥92% or ≥95% on room air was similar across treatment groups in Cohort 1 as well as in the subgroup with symptom onset ≤3 days. However, SpO_2 was not measured at room air during oxygen supplementation.

- In Cohort 1, the median (95% CI) time to protocol-defined clinical stability considering SpO_2 ≥92% or ≥95% based on KM analysis was longer in the rilematovir low dose and high dose groups compared to the placebo group (5.09 [2.17; 6.89] days and 6.69 [3.00; 10.31] days in the rilematovir low dose and high dose groups, respectively, compared to 3.54 [2.32; 6.43] days in the placebo group). However, in the subgroup with symptom onset ≤3 days, that time to clinical stability was approximately 1.5 days shorter in the active treatment groups than in the placebo group (5.26 [1.92; 8.20] days and 5.32 [1.83; 10.78] days in the rilematovir low dose and high dose groups versus 6.84 [3.92; 28.90] days in the placebo group).

- Few participants in Cohort 1 were admitted to the ICU post-baseline (2, 1, versus 1 in the low and high rilematovir dose groups and placebo, respectively). The 1 participant in the high dose group was in the subgroup with symptom onset ≤3 days.

- Investigator-determined RSV-related complications, derived from the adverse event (AE) reports, were reported for 8/36 of participants in the rilematovir low dose group, 12/37 of participants in the rilematovir high dose group, and 11/38 of participants in the placebo group. Most complications were of respiratory nature. Complications of Grade 3 to 4 were reported in 3, 1, and 4 participants in the rilematovir low and high dose and in the placebo group, respectively. In the subgroup with symptom onset ≤3 days, complications were reported for 2/17 participants in the rilematovir low dose group, 5/16 participants in the rilematovir high dose group, and 5/18 participants in the placebo group. Complications of Grade 3 to 4 were reported in 0, 1, and 3 participants in the rilematovir low and high dose and in the placebo groups, respectively. No Grade 4 RSV-related complications were reported.

- The ordinal RSV Recovery Scale (RRS) provides 7 mutually exclusive conditions ordered from best (home without symptoms based on the ObsRO Signs/Symptoms) to worst (death), and the score reflects the participant's worst status on the day of assessment. The first day on which 50% of participants was in either of the 2 home categories was on Day 6, considering all participants in the rilematovir high dose and the placebo groups. The observed common odds ratio was 0.38 (0.11; 1.33) including all participants, and 0.58 (0.16; 2.11) excluding participants in the ICU at Day 1 before first dosing. The odds for a better clinical outcome are 62% to 42% lower under placebo than under rilematovir.

- The proportion of participants resolved defined as not needing either oxygen or feeding/hydration supplementation, not requiring ICU, and Key RSV Signs/Symptoms

(based on ClinRO Signs/Symptoms) resolved (absent or mild) was analyzed over time. As of Day 4, the proportion of participants resolved was greater in both the low and high rilematovir dose groups than in the placebo group and greatest in the rilematovir high dose group. At Day 6 (the same day at which the RRS was evaluated), the proportion of participants resolved was 47.1% (8/17) and 62.5% (10/16) in the rilematovir low dose and high dose groups, respectively, compared to 33.3% (6/18) in the placebo group. Using the modified imputation rule, the proportion of participants resolved at Day 6 was 35.3% (6/17) and 56.3% (9/16) in the rilematovir low dose and high dose groups, respectively, compared to 33.3% (6/18) in the placebo group.

- For the time to resolution taking into account resolution of Key RSV Signs/Symptoms (based on ObsRO Signs/Symptoms) (using an alternative definition of "resolved" in combination with 24 hours supplementation-free), the KM medians demonstrated a reduction of 40% for the rilematovir high dose versus placebo group (6.48 [4.00; 11.84] days compared to 10.83 [7.12; 13.93] days, respectively).

- The time to resolution of Key RSV Signs/Symptoms (based on ObsRO Signs/Symptoms) after discharge was 3 days shorter for the rilematovir high dose group compared to the placebo group (0.92 [0.51; 2.72] days compared to 4.16 [0.91; 6.78] days, respectively).
- The time to resolution of Key RSV Signs/Symptoms including supplementation-free for 12 hours based on ClinRO Signs/Symptoms was similar for the rilematovir high dose and placebo groups (6.60 [2.67; -] days and 6.85 [3.79; 12.86] days, respectively).
- No difference was observed in the time to end of oxygen supplementation up to 72 hours from first discharge (2.80 [1.21; 5.65] days in the rilematovir high dose group compared to 3.10 [0.98; 5.62] days in the placebo group).
- The time to end of supplementation (oxygen and feeding/hydration) up to 72 hours from first discharge was 1 day shorter for the rilematovir high dose group compared to the placebo group (2.80 [1.21; 6.00] days compared to 4.04 [2.32; 6.02] days, respectively).

Safety and Tolerability

Adult Population

Phase 1 Safety Pooling

For the purpose of reviewing the available clinical safety data from adult healthy volunteers, data from Phase 1 studies 64417184RSV1003, 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, 53718678RSV1006, 53718678RSV1007, 53718678RSV1008, and 53718678RSV1009 were pooled at the time of the cut-off for the IB Ed 7.[26] Overall, during these clinical studies, single doses up to 1,000 mg rilematovir and multiple doses up to 500 mg rilematovir qd and 250 mg rilematovir bid were generally safe and well tolerated. These studies did not identify any safety signal for rilematovir. No deaths or other serious adverse events (SAEs) were reported.

Among participants who received multiple doses of rilematovir alone, 52.9% experienced a TEAE as compared to 66.7% of all participants who received placebo. All the treatment-emergent AEs (TEAEs) reported during these studies were either Grade 1 or Grade 2 in severity. Treatment-emergent AEs reported more frequently (difference in incidence of ≥10% in the all rilematovir alone + with interacting drug group) in participants who had received at least 1 dose of rilematovir compared to participants who received placebo included fatigue, headache, and hot flush.

Based on exposure-response analysis in Study 53718678RSV1009, an important potential risk of QT interval prolongation was identified for rilematovir. For more details on the analysis, refer to the IB.[26] A change to a bid dosing regimen (see Section 4.3) and several other mitigation measures to safeguard the participants (see Section 2.3.3) have been implemented.

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 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 msec] 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) (the rilematovir and placebo oral solution contains 30% HP-β-CD as 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

Interim analysis results (data cut-off 23 September 2019, N 67) 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 SAEs, and no AEs of severity Grade 3 or 4 in the study. Overall, 55.6% of participants experienced at least 1 TEAE, of which diarrhea was the most frequently reported TEAE. The overall incidence of TEAEs was smaller in the rilematovir 500 mg group (36.4%) than in the placebo group (59.1%). The highest incidence rate of TEAEs was observed in rilematovir 80 mg group (73.9%). The incidence of TEAEs leading to study medication discontinuation was higher in rilematovir 500 mg group (13.6%) than in rilematovir 80 mg group (8.7%), or the placebo group (4.5%). There were 2 participants (in rilematovir 500 mg group) with AE (diarrhoea) leading to permanent study discontinuation. 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.

Pediatric Population

Overall, treatment with rilematovir was generally safe and well tolerated in pediatric participants and no safety signals arose in pediatric participants compared to the previously established safety profile in adults.

Study 53718678RSV1005

In Study 53718678RSV1005 in hospitalized pediatric participants receiving the oral solution formulation, no deaths, Grade 4 AEs, or AEs leading to study discontinuation or permanent discontinuation of study intervention were reported. Four SAEs were reported, 2 in the rilematovir (combined) treatment group (rhinitis and bronchiolitis) and 2 in the placebo group (pneumonia and bronchiolitis). These were reported as serious because of rehospitalization and were considered by the investigator to be not related to the study intervention. The majority of participants were reported with at least 1 AE, at similar incidence rates in both treatment arms (28/37 participants [75.7%] in the rilematovir [combined) treatment group vs 6/7 participants [85.7%] in the placebo group, respectively). Most of the reported AEs were Grade 1 or Grade 2 in severity. Two Grade 3 (severe) AEs were reported (both bronchiolitis; 1 each in the rilematovir [combined] and placebo group, both were also reported as SAEs). By dictionary-derived term, most frequently reported AEs in participants treated with rilematovir (reported in ≥10% of participants) were vomiting, URTI, and feces soft.

Treatment-emergent laboratory abnormalities were infrequently reported and of low severity (maximal Grade 2). None were observed more frequently (difference in incidence of ≥5%) in the rilematovir (combined) group compared to the placebo group.

No clinically relevant differences in incidence rates of vital signs abnormalities were observed between rilematovir and placebo. ECG abnormalities were scarce and generally not considered clinically relevant. No dose-relationship was observed for the AEs, or abnormalities in laboratory or ECG parameters or in vital signs.

Overall, treatment with rilematovir was generally safe and well tolerated and no new safety signals arose compared to the overall safety profile in adults.

Study 53718678RSV2002

In the interim analysis (data cut-off 02 January 2020) of the ongoing Study 53718678RSV2002 in pediatric participants hospitalized (Cohort 1) and non-hospitalized (Cohort 2) with RSV infection, no deaths, Grade 4 AEs, or AEs leading to premature termination of study medication or study participation were reported. Emergent SAEs were reported in 9.6% (5/52) of participants in the rilematovir low dose group, 3.8% (2/52) in the rilematovir high dose group, and 9.8% (5/51) in the placebo group, of which most were Grade 3 in severity. None of these SAEs were considered related to study treatment by the investigator and all participants recovered from their SAE within the study period. The majority of participants (approximately 65%) in all treatment groups were reported with at least 1 emergent AE (EAE). Most of the EAEs (>55%) were reported as Grade 1 or 2 (mild to moderate in severity) in all treatment groups. Grade 3 (severe) EAEs were reported for 11.5% (6/52) of participants in the rilematovir low dose group, 3.8% (2/52) in the rilematovir high dose group, and 7.8% (4/51) in the placebo group. None of these Grade 3 EAEs were considered at least possibly related to study treatment by the investigator.

By system organ class, the most frequently (>10% in any treatment group) reported EAEs were infections and infestations; respiratory, thoracic and mediastinal disorders; skin and subcutaneous disorders; gastrointestinal disorders; and blood and lymphatic system disorders. By preferred term, the most frequently reported EAEs (>5.0% in any treatment group) were nasopharyngitis, URTI, dermatitis diaper, rash, diarrhea, vomiting, faeces soft, thrombocytosis, and pyrexia.

Emergent AEs that were considered to be at least possibly related to the study medication by the investigator were reported for 5.8% (3/52) of participants in the rilematovir low dose group (diarrhea, vomiting, and gastroenteritis in one participant each), 3.8% (2/52) of participants in the rilematovir high dose group (diarrhea and urticaria in one participant each), and 11.8% (6/51) of participants in the placebo group (diarrhea and feces soft in one participant; diarrhea in 2 participants; feces soft, rash, and transaminases increased in one participant each). All these EAEs were Grade 1, except for one EAE which was Grade 2 diarrhea in one placebo participant.

Treatment-emergent laboratory abnormalities were infrequently reported of which most were Grade 1 or 2. No relevant differences were seen between the rilematovir treatment groups and the placebo group. The incidences of graded abnormalities for alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin as well as for activated partial thromboplastin time (aPTT) and prothrombin time (PT) were low (ie, reported for at most 1 participant in any rilematovir treatment group).

No clinically relevant differences in incidence rates of vital signs abnormalities were observed between rilematovir and placebo. ECG abnormalities were scarce and generally not considered

clinically relevant. No changes from baseline in QTcF or QT interval corrected for heart rate according to Bazett's formula (QTcB) of >60 msec were reported. No relevant differences between the rilematovir treatment groups and the placebo group were seen for the changes from baseline in QTcF or QTcB intervals.

Overall, treatment with rilematovir was generally safe and well tolerated. Overall, no dose-relationship was observed for the AEs, or abnormalities in laboratory or ECG parameters or in vital signs. No new safety signals arose compared to the previously established safety profile.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of rilematovir may be found in the IB.[26]

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.

At the time of protocol writing, a total of 345 adult and 192 pediatric participants received at least 1 dose of rilematovir. Of the 345 adult participants, 251 received at least 1 dose of rilematovir ≥500 mg. In total, approximately 92 pediatric participants received multiple ≥500 mg adult dose equivalents.

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 is limited, the sponsor considers hepatobiliary effects to be a safety topic of special interest and hepatobiliary function will be monitored by routine hepatobiliary function tests during clinical studies.

Review of data of the TQT Study 53718678RSV1009, has identified a new important potential risk of QT prolongation for rilematovir (see Section 2.2 and the IB[26] for more information). Therefore, a change in dose regimen (see Section 4.3) and several other measures to safeguard the participants (see Section 2.3.3) have been implemented.

Overall, the oral suspension formulation used in Part 1 and 2 of the TQT study was generally safe and well tolerated in these 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. However, exposure-response analysis based on time-matched QTc Holter data demonstrated that, following a single dose of 500 mg, the effect of rilematovir on cardiac repolarization is not of regulatory concern,[25] but at doses ≥1,000 mg an increase of placebo-corrected change from baseline for the individual-corrected QT interval (ΔΔQTcI) above the threshold of 10 msec can be expected (Section 2.2).

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

Study procedures such as blood sampling carry a potential risk (eg, pain, discomfort, hematoma) to the participant. Therefore, minimal volumes of blood (by venipuncture or by finger or heel prick with capillary blood collection) for both safety and PK assessments will be sampled only at carefully selected timepoints. Investigators may use local anesthetics prior to sampling.

The evaluation of rilematovir antiviral activity and sequencing requires nasal MT 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 nose bleeding can occur. Examples of other AEs that may occur, but are not considered serious, are: coughing, gagging, nausea, and vomiting.

Investigational staff should take the customary measures to ensure that study-specific assessments such as blood sampling or nasal swabbing are performed with as little additional stress as possible for the participant. Investigators may use local anesthetics prior to blood sampling.

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).

Despite a limited data set, particularly in the placebo arm, a trend towards an early antiviral effect of rilematovir was observed in the pediatric population based on data from Study 53718678RSV1005 (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 children ≥28 days 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.

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.

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

2.3.2.2. Potential Benefits

Participants participating in this study may benefit through improvement of the clinical course of their RSV infection. Treatment with rilematovir could reduce the severity and duration of RSV signs/symptoms, and their impact on functioning, reduce the effect of RSV infection on physiologic parameters, prevent progression to more severe disease status, reduce the need for and duration of supportive care (eg, oxygen supplementation, intravenous (IV) fluids/feeding, days of hospitalization), and accelerate the participant's 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 the ongoing pediatric Study 53718678RSV2002, the interim analysis 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.

In the adult Study 53718678RSV2004, the interim analysis data demonstrated a positive trend for time to symptom resolution of Key RSV Signs/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.

The unequal randomization (2:1 active: placebo in each age group) affords the majority of participants the potential benefit of rilematovir treatment.

2.3.3. Benefit-Risk Assessment for Study Participation

Currently only limited options are available for the treatment of RSV infection (see Section 2.1). Based on the available data and proposed safety measures, the overall benefit-risk balance for participation in this study is considered favorable because:

- Antiviral effect proof-of-concept was established in adult healthy volunteers challenged with a laboratory strain of RSV (Study 53718678RSV2001), in non-hospitalized adult participants infected with RSV (interim analysis of Study 53718678RSV2004), as well as in RSV-infected pediatric participants (Study 53718678RSV1005) (Section 2.2).
- Data from an interim analysis of Study 53718678RSV2002 in RSV-infected pediatric participants showed benefits for clinical course outcomes and antiviral effects, particularly in the subgroup of participants with symptom onset ≤3 days, as planned for enrollment in this study (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);
- No safety concerns were identified in the interim analysis of 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);
- Several safety measures have been proposed to minimize potential risk to participants, including:

  Only participants who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol, Sections 5.1 and 5.2) will be allowed to participate in the study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of the participants in the study.

  Neonates will only be enrolled in the main study after recommendation from the independent data monitoring committee (IDMC) based on results from a substudy in neonates.

  Utilization of study intervention discontinuation criteria and study stopping criteria (see Sections 7.1 and 7.2).

  Participants are to be hospitalized before treatment initiation, allowing for intensive monitoring of participants at the beginning of the study until discharge. After discharge from the hospital and for the remainder of the study period, a close follow-up (see Schedule of Activities) is planned with on-site visits on Day 3, Day 5, Day 8, Day 14, Day 21, and a phone follow-up/conditional on-site visit on Day 35, when the participant completes the study.

  Safety surveillance in this study will monitor standard safety parameters associated with investigational drug development (see Section 8.2) and safety topics of special interest of rilematovir (see Section 8.3.5) as part of the study assessments.

  Safety surveillance will be performed in a manner that minimizes the total number of required invasive procedures (eg, blood draws) to minimize discomfort to study participants.

  Utilization of results from diagnostic testing (swab) performed as part of SOC.

  The establishment of an IDMC (see Section 9.6) to monitor data on a regular basis to ensure continuing safety of the participants enrolled in the study.

  Customary measures taken by investigational staff to ensure that study-specific assessments such as blood sampling and nasal swabbing are performed with as little additional stress as possible for the participant and allowance of the use of local anesthetics prior to blood sampling.

- 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 bid dose regimens which, relative to the respective qd 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).

  Specific cardiovascular and ECG-based criteria were established for eligibility assessment (see Section 5.1 and 5.2).

Close monitoring of the use of concomitant medications will be conducted regularly. Drugs that are moderate or strong CYP3A4 inhibitors and/or BCRP inhibitors will be disallowed (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).

Evaluation of clinical status, AEs, vital signs, physical examination as well as laboratory parameters will be conducted as per the Schedule of Activities. Additional unscheduled visits may be performed based on the overall clinical picture as per the investigator's clinical discretion.

Utilization of study intervention discontinuation and withdrawal criteria specific to QT interval changes (see Section 7.1).

Rapid correction of any hypokalemia and/or hypomagnesemia during treatment period, and check by the investigator of the use of concomitant QT prolonging drugs (see Section 8.3.5.2).

Specific toxicity management for cardiac and ECG related events was established (see Section 8.3.5.2).

Considering the measures taken to minimize risk to participants of this study, the potential risks identified in association with participation in this study and rilematovir are justified by the anticipated benefits that may be afforded to participants infected with RSV.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the clinical outcome on the RRS.	• RRS[a] as assessed on the first study day when at least 50% of the participants across treatment arms are discharged from the hospital (the study day for the RRS evaluation will be determined based on blinded data at the first interim analysis by an independent statistician).
Secondary	
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to clinical resolution of RSV disease.	• Proportion of participants clinically resolved from RSV disease based on ClinRO Signs/Symptoms[c,e] as assessed on the same study day as the primary endpoint.
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the time from first dosing to resolution of Key RSV Signs/Symptoms[b] including supplementation free.	• Time from first study dose to resolution of Key RSV Signs/Symptoms (absent or mild)[d,e] based on parent's/caregiver's ObsRO Signs/Symptoms and supplementation free (oxygen and feeding/hydration) for at least 24 hours.
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the time from discharge to resolution of Key RSV Signs/Symptoms.	• Time from discharge to resolution of Key RSV Signs/Symptoms[d,e] based on ObsRO Signs/Symptoms (only including participants who did not reach resolution before first discharge).
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the time from first dosing to end of oxygen supplementation.	• Time from first dosing to end of oxygen supplementation (only including participants who were receiving oxygen supplementation at the time of first dosing).
• To evaluate the superiority of rilematovir compared to placebo treatment with respect to the incidence of post-baseline RSV-related complications.	• Incidence in post-baseline RSV-related complications.
• To evaluate the safety and tolerability of rilematovir.	• Safety and tolerability, as assessed by AEs, clinical laboratory testing, ECGs, vital signs throughout the study.
• To evaluate the effect of rilematovir on the clinical course of RSV disease as assessed electronically by ObsRO Signs/Symptoms and ObsRO General Health Questions (GHQ).	• The following endpoints will be based on the ObsRO Signs/Symptoms: ♦ time to resolution of signs/symptoms (absent or mild)[e] of RSV disease; ♦ actual values and changes from baseline in scores.

Objectives	Endpoints
	• The following endpoint will be based on the ObsRO GHQ: ♦ time to improvement.
• To evaluate the effect of rilematovir on the clinical course of RSV disease as assessed electronically by ClinRO Signs/Symptoms and ClinRO GHQ.	• The following endpoints will be based on the ClinRO Signs/Symptoms: ♦ time to resolution of signs/symptoms (absent or mild)[e] of RSV disease; ♦ actual values and changes from baseline in scores; ♦ proportion of participants clinically resolved from RSV diseases based on ClinRO Signs/Symptoms[c,e] as assessed each day from Day 2 to 8. • The following endpoint will be based on the ClinRO GHQ: ♦ general impression of change.
• To evaluate the effect of rilematovir on the clinical course of RSV disease (other than ClinRO and ObsRO assessments).	• RRS[a] as assessed each day separately from Days 2 to 8. • Time to hospital discharge from start of dosing. • Time to readiness for hospital discharge. • Proportion of participants requiring intensive care unit (ICU) stay. • Duration of requiring ICU stay. • Proportion of participants requiring rehospitalization for respiratory/other reasons. • Proportion of participants requiring oxygen supplementation. • Duration of oxygen supplementation. • Time to end of supplemental feeding/hydration. • Proportion of participants requiring hydration and/or feeding by intravenous (IV) administration or nasogastric tube. • Duration of supplemental feeding/hydration. • Time to end of supplementation (oxygen and/or feeding/hydration). • Number and type of medical encounters. • Incidence of antibiotic treatment episodes. • Incidence of systemic or inhaled corticosteroids and bronchodilators use.
• To evaluate the antiviral effect of rilematovir as measured by RSV viral	• RSV viral load (area under the RSV viral load-time curve [AUC]) from immediately prior to first dose of

Objectives	Endpoints
load in nasal mid-turbinate (MT) swab samples by qRT-PCR assay.	study intervention (baseline) through Day 3, Day 5, and Day 8. • RSV viral load and change from baseline over time. • Proportion of participants with undetectable RSV viral load at each time point of assessment throughout the study.
• To evaluate the emergence of mutations in the viral genome potentially associated with resistance to rilematovir.	• Sequence changes (post-baseline) in the RSV F gene compared to baseline.
• To evaluate the PK of rilematovir.	• PK parameters of rilematovir.
• To explore the PK/pharmacodynamic (PD) relationships of rilematovir for efficacy and safety.	• PK/PD analysis of PK of rilematovir and selected primary and secondary efficacy and safety parameters.
• To evaluate the acceptability and palatability of the rilematovir formulation.	• Acceptability and palatability of the rilematovir formulation as assessed through a questionnaire.
Exploratory	
• To explore other effects of rilematovir on the clinical course of RSV disease.	• Time from first dosing to SpO_2 ≥92% on room air among participants who were not on oxygen supplementation prior to the onset of respiratory signs/symptoms. • Respiratory rate, heart/pulse rate, body temperature, and SpO_2 over time as measured by the investigator (during scheduled visits). • Proportion of participants with signs/symptoms of RSV disease at discharge according to last ClinRO Signs/Symptoms evaluation prior to discharge. • The ClinRO Signs/Symptoms score for each sign/symptom according to last evaluation prior to discharge in those participants not resolved at discharge.
• To explore the effect of rilematovir on the impact of the child's RSV disease on the parent(s)/caregiver(s) and family based on the PRESORS Caregiver Impact Questions.	• Extent of the parent's/caregiver's worry about the child's health. • Time missed from usual activities by the parent/caregiver. • Time missed from work by anyone in child's household due to the child's illness.
• To explore the relationship between antiviral activity and the primary and key secondary clinical outcomes.	• RSV viral load based endpoints and primary and key secondary clinical course endpoints.

Objectives	Endpoints
• To explore the evaluation of biomarkers associated with RSV or treatment effects (optional).	• Specific biomarkers in leftover blood samples and nasal MT swabs (optional).

a. For details on the RRS see Section 8.1.1.1.
b. Signs are defined as objective evidence of the disease, which are apparent to the physician during examination (such as tachycardia, tachypnea, chest wall retractions, grunting, and nasal flaring). Symptoms are defined as subjective manifestations of the diseases, reported by the participant or by the parent(s)/caregiver(s), but not necessarily apparent to the physician during examination (such as rhinorrhea, cough, feeding difficulties, disturbed sleep, and disturbed activity level). Throughout this protocol, the notation "signs/symptoms" is used.
c. Clinical resolution is defined by: free of oxygen supplementation, AND free of supplemental feeding, AND not requiring ICU, AND Key RSV Signs/Symptoms resolved to absent or mild as per the ClinRO Signs/Symptoms (see also Section 8.1.1.2).[e]
d. Key RSV Signs/Symptoms are: Breathing problems, retractions, tachypnea, cough, wheezing (ClinRO Signs/Symptoms only), breathing sounds (ObsRO Signs/Symptoms only), and tachycardia (see also Section 8.1.1.3).
e. See Section 10.14, Appendix 14 and Section 10.15, Appendix 15 for definitions of resolved/not resolved.
f. See Section 8.1.1.2 for the list of complications assessed.

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that treatment with rilematovir improves clinical outcome of RSV infection as compared to placebo in hospitalized pediatric participants as assessed with the RRS on the first study day when at least 50% of the participants across treatment arms are discharged from the hospital.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, interventional study in infants and children (≥28 days to ≤5 years of age) and subsequently in neonates (<28 days of age), hospitalized (refers to having planned at least 24 hours with an overnight stay in the hospital) with RSV infection. The substudy at specific sites will be initiated only after positive recommendation by the IDMC upon review of interim analysis 1 results of the main study (see also Sections 9.5 and 9.6). "Subsequently in neonates" refers to the main study being opened for enrollment of neonates at all sites following completion of a prior substudy in neonates, IDMC review of the substudy data, and positive recommendation. This protocol only describes the main study. The specifics to the substudy will be described in a separate substudy protocol. Investigators and relevant health authorities, ethics committees, and institutional review boards (IRBs) will be informed in writing of the decision and the selected dosing regimen for neonates.

A target of 737 hospitalized RSV-infected participants will be randomized in a 2:1 ratio to receive either rilematovir or placebo bid.

Study participants with signs/symptoms of an acute respiratory illness supporting a diagnosis of RSV infection (see Table 1) will be identified and tested for RSV infection when they are

hospitalized or present to the ER/clinic and are expected to be hospitalized. Participants should only be screened if they are expected to be randomized within ≤3 days of RSV sign/symptom onset (see RSV Symptom Onset to Randomization Calculator in Section 10.17, Appendix 17). During screening, a nasal MT swab will be collected for local diagnosis of RSV infection using a molecular-based assay (PCR or other) and for additional post-hoc analysis at a central laboratory to determine the RSV viral load (and subtype), and viral sequencing. A SOC sample that is collected within 24 hours prior to screening start and results in an RSV positive diagnosis may also be used to determine study eligibility. In such case, the collection of the study-specific nasal MT swab at screening is not required (see also Figure 3).

Participants with RSV disease (ie, at least 1 sign/symptom of URTI, at least 1 sign/symptom of LRTI, and at least 1 systemic/general sign/symptom [see Table 1 and Section 5.1, Inclusion Criteria]) will be enrolled. Cough or wheezing cannot be the only LRTI sign/symptom present, ie, at least one other LRTI sign/symptom needs to be present for eligibility. Eligible participants can be otherwise healthy or have (a) risk factor(s) for severe RSV disease (as defined in Table 2). Those who are immunocompromised and those with neuromuscular diseases that affect swallowing or the thoracic muscles are excluded from participation.

Table 1: RSV Disease Signs/Symptoms for Eligibility

Upper Respiratory Tract Infection (URTI) Signs/Symptoms:
Nasal congestion
Rhinorrhea
Lower Respiratory Tract Infection (LRTI) Signs/Symptoms:
Increased respiratory efforts, evidenced by:
– subcostal, intercostal, or tracheosternal retractions
– grunting
– head bobbing
– nasal flaring
– tachypnea
Wheezing[a]
Cyanosis
Cough[a]
Apnea
Systemic / General Signs/Symptoms:
Feeding difficulties (defined as <75% intake of normal food amounts)
Dehydration
Fever
Disturbed sleep
Disturbed activity level (irritable, restless, agitated, or less responsive)

[a] Cough or wheezing cannot be the only LRTI sign/symptom present, ie, at least one other LRTI sign/symptom needs to be present for eligibility.

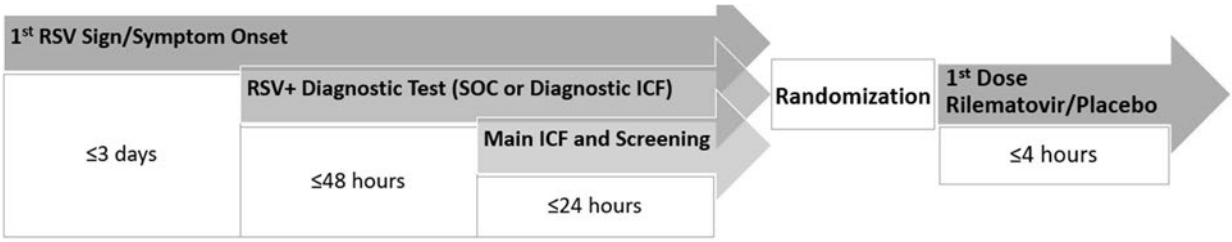
Table 2: Risk Factors for Severe RSV Disease

Prematurity at birth[a]
Bronchopulmonary dysplasia
Congenital heart disease
Down syndrome
Neuromuscular impairment[b]
Cystic fibrosis
Recurrent wheezing[c]
Asthma
Other congenital disease

[a] ***Note:*** Prematurely born participants are only eligible for this study if their age corrected for gestational age at birth is ≥28 days at the time of consent.[1] After this main study opens to neonate enrollment: prematurity is not allowed for neonates (ie, neonate participants should have been born at term, after at least 37 weeks of gestation).
[b] Excluding neuromuscular diseases that affect swallowing or the thoracic muscles.
[c] Recurrent wheezing is defined as ≥1 episode of wheezing without a cold in the past year.[22]

Randomization should occur within a maximum of 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first, and no later than 3 days after RSV sign/symptom onset (see Figure 2). Randomization will be stratified by presence of risk factors for severe RSV disease (otherwise healthy vs presence of [a] risk factor[s] for severe RSV disease, see Table 2) and by region (Asia-Oceania, EMEA, Northern America, and Latin America-The Caribbean).

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



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

Study intervention administration should start as soon as possible, but no later than 4 hours after randomization (see Figure 2). Dosing will be based on a mg/kg basis per age group and 4 age groups are defined based on the participant's age at the time of consent (see Table 3). Study intervention (oral suspension) will be administered orally, bid, with a treatment duration of 7 days (14 consecutive doses) (see also Section 6).

Table 3: Age Groups and Dosing Regimen

Age Group	Age Range	Dosing Regimen
Age group 1	≥28 days to <3 months of age (ie, 28 to 91 days of age, extremes included)	2.5 mg rilematovir/kg bodyweight bid
Age group 2	≥3 months to <6 months of age (ie, 92 to 182 days of age, extremes included)	3 mg rilematovir/kg bodyweight bid
Age group 3	≥6 months to ≤5 years of age (ie, 183 to 1,826 days, extremes included)	4.5 mg rilematovir/kg bodyweight bid
Age group 4[a]	at term birth (ie, after at least 37 weeks of gestation) to <28 days of age (ie, 1 day to 27 days, extremes included)	XX mg[b], rilematovir/kg bodyweight bid, dependent on outcome of substudy and following IDMC recommendation

bid = twice daily; IDMC = Independent Data Monitoring Committee.

Note: The above-mentioned doses refer to the amount of JNJ-53718678-AAA (free form); 20 mg JNJ-53718678-AAA corresponds to 23 of mg JNJ-53718678-ZCL (hemi-tartrate of JNJ-53718678-AAA).

[a] After opening of recruitment in neonates in the main study dependent on positive IDMC recommendation after completion of a substudy in neonates (see Section 9.6).

[b] The dosing regimen will not exceed the exposures simulated for the bid regimen in pediatric subjects ≥28 days to ≤5 years of age and observed for the 250 mg bid regimen in adults.

All participants will receive standard supportive care for RSV infection as per local SOC but considering the restrictions provided in Section 6.8. All SOC intervention should be recorded as concomitant medication/treatment on designated electronic case report form (eCRF) pages.

The study will include a Screening Period (Day -1 to Day 1), a Treatment Period (Day 1 to Day 8), and a Follow-up Period (Day 9 to Day 35 [±3]). The total study duration for each participant will be approximately 36 days (Screening included).

Participants can be discharged as of Day 2, if deemed appropriate by the investigator and after completion of the required investigator-performed assessments for that day, with exception of the PM bid assessments. Parent(s)/caregiver(s) of discharged participants are required to follow the Schedule of Activities as outlined in Section 1.3.2.

The clinical severity and clinical course of RSV infection will be assessed through different measures (see Section 8.1.1).

The PRESORS developed by the sponsor include several assessments that the clinicians treating the study participants and the parents/caregivers of participants need to complete on an electronic device at the timepoints specified in the Schedule of Activities. The PRESORS for the clinicians consists of the ClinRO Signs/Symptoms, the ClinRO GHQ, and an additional question regarding apnea (see Section 10.13, Appendix 13). The PRESORS for the parents/caregivers (PRESORS ObsRO) consist of ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Information (only assessed during set up of the electronic device) (see Section 10.10, Appendix 10, Section 10.11, Appendix 11, and Section10.12, Appendix 12). The sponsor developed the ClinRO and ObsRO Signs/Symptoms assessments to monitor signs/symptoms of RSV disease severity observed and rated by the clinicians treating the pediatric participants as well as by the participant's parent(s)/caregiver(s) from baseline through end of follow-up. Clinicians and parent(s)/caregiver(s) are instructed to rate each RSV sign/symptom at its worst during the recall

period. The ClinRO and ObsRO GHQs provide assessments by the clinicians and the parent(s)/caregiver(s), respectively, of the overall impression of the participant's RSV disease severity, change in the participant's RSV disease, and overall health status. In addition to the ObsRO Signs/Symptoms and ObsRO GHQ, parents/caregivers will also be asked to complete Caregiver Impact Questions and an assessment of acceptability and palatability at the timepoints specified in the Schedule of Activities on the same electronic device. Refer to Section 8.1.1.3 for more information on ClinRO and ObsRO Clinical Outcome Assessments and Caregiver Impact Questions.

Antiviral activity and viral sequencing will be evaluated as described in Sections 8.1.2 and 8.1.3, respectively.

Safety and tolerability, including AEs, laboratory assessments, ECGs, vital signs, and (directed) physical examinations will be assessed throughout the study from signing of the main informed consent form (ICF) until the participant's last study-related activity (see Sections 8.2 and 8.3).

Pharmacokinetic assessments during the study will be based on sparse sampling to limit the number of pricks (2 samples, see Section 1.3.3, Pharmacokinetic Assessments Sampling Schedule) and will be analyzed using a popPK model as described in Section 8.4.

Medical encounters and acceptability and palatability of the study intervention will be assessed as described in Sections 8.6 and 8.7.

Residuals of blood and nasal MT swab samples collected during the study may be used for exploratory biomarker analyses as described in Section 8.8.

The presence of other respiratory viruses or bacteria will be assessed as described in Section 8.9.

See Section 10.19, Appendix 19 for guidance on study conduct during the COVID-19 pandemic.

An IDMC will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3 for details.

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

4.2. Scientific Rationale for Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of rilematovir in infants and children (≥28 days to ≤5 years of age) and subsequently including neonates (born at term, <28 days of age) after completion of the substudy (see Section 9.6), hospitalized with acute respiratory tract infection due to RSV. The results of this study aim to obtain efficacy and safety data to support the registration of rilematovir for treatment of RSV infection in pediatric patients.

Blinding, Control, Study Phase/Periods, Intervention Groups

There is currently no approved antiviral treatment routinely used for the treatment of RSV infection. 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. 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 2:1 to receive either rilematovir or placebo (see Section 4.1). The unequal randomization (2:1 active: placebo in each age group) affords the majority of participants the potential benefit of rilematovir treatment. For dosing purposes, 4 age groups (at term birth to <28 days of age, ≥28 days and <3 months; ≥3 months and <6 months; ≥6 months and ≤5 years of age) are defined depending on the participant's age at the time of consent, taking into account the abundance of specific enzymes (and their maturation) involved in the metabolism of rilematovir in these different age groups.

Stratification Factors

Randomization will be stratified by presence of risk factors for severe RSV disease (otherwise healthy versus presence of [a] risk factor[s] for severe RSV disease as defined above, see Table 2) and by region to ensure even balance across intervention groups.

Presence or absence of (a) risk factor(s) for severe RSV disease is included as stratification factor due to potentially different (more severe) disease course of RSV infections in patients with these conditions.

Region is included as stratification factor due to regional differences in health care systems and standard-of-care practices.

Study Population

Hospitalized patients in the age group 1 day to ≤5 years are targeted, as they are most affected by severe RSV disease. Hospitalized patients are targeted as RSV-related LRTI is a major cause of hospital admissions and they are at the highest risk of developing RSV-related complications. See Section 2.1 for more information. Patients with risk for severe RSV disease are enrolled, as they have a high medical need for an effective treatment.

Study and Dosing Duration

The total study duration for each participant will be approximately 36 days (Screening included). Dosing will last for 7 days (14 consecutive doses) as it has been shown that the duration of viral

shedding upon 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 Study 53718678RSV2004 (non-hospitalized RSV-infected adults) and in the completed Study 53718678RSV1005 in pediatric participants, and was generally safe and well tolerated. In addition, the same dosing duration is being evaluated in the ongoing Study 53718678RSV2002 (hospitalized and non-hospitalized RSV-infected pediatric participants ≥28 days and ≤3 years of age). The interim analysis results of this study showed that the dosing duration was generally safe and well tolerated.

Clinical Outcomes of RSV Treatment

Treatment with rilematovir may reduce the severity and duration of RSV signs/symptoms, and their impact on functioning, the effect of RSV infection on physiologic parameters, prevent progression to more severe disease status, reduce the need for and duration of supportive care (eg, oxygen supplementation, IV fluids/feeding, days of hospitalization), and accelerate the participants' return to pre-RSV health status.

The interim analysis of Study 53718678RSV2002 demonstrated a trend towards an improvement of the clinical course of RSV disease in children ≥28 days and ≤3 years of age with RSV disease, with more pronounced effects in the subgroup with symptom onset ≤3 days.

This study will evaluate the impact of treatment with rilematovir on the clinical course of RSV disease and on clinically relevant changes in patient status over meaningful defined levels of improvement/resolution using a multipoint scale at a clinically relevant timepoint as defined at the first interim analysis based on blinded data across treatment arms (ie, the study day when at least 50% of participants across treatment arms are discharged from the hospital).

RSV Disease Presentation in the Study Population

In a retrospective study, a total of 5,483 pediatric patients (≤14 years old) hospitalized with acute respiratory tract infection, 710 of the 729 (97.4%) RSV-positive patients were children under 5 years old.[32] The clinical manifestations ranged from mild URTI or otitis media to severe and potentially life-threatening LRTI. The most common form of LRTI in RSV-infected infants was bronchiolitis, but pneumonia and croup were also seen. Involvement of the lower airways occurred in ~15 50% of infants and young children with primary RSV infection and required hospitalization in 1 3 % of the annual birth cohort, with infants between 2 and 6 months of age being at the highest risk. However, in some regions, the highest incidence of LRTI was reported in infants aged 6 11 months or even children between 1 and 2 years of age.

Assessed Key RSV Signs/Symptoms

For the primary and key secondary endpoints of this study, a "resolved/not resolved" scoring of Key RSV Signs/Symptoms as assessed by the ClinRO Signs/Symptoms and ObsRO Signs/Symptoms is used. These Key RSV Signs/Symptoms are: Breathing problems, retractions, tachypnea, cough, wheezing/breathing sounds, and tachycardia. These Key RSV Signs/Symptoms

were selected as the most relevant and important indicators of LRTI associated with clinically important RSV disease that can be observed by a child's parent/caregiver without the need for medical technology or training. They were selected based on qualitative research and content validity work, including clinical expert review, caregiver interviews, review of published studies, literature research, and results from previous studies.

The same Key RSV Signs/Symptoms will be assessed across all age groups. While some of the signs/symptoms are recognized to be more prevalent in certain age groups compared to other age groups, and there are age-specific criteria for defining abnormal ranges for some signs/symptoms, the same Key RSV Signs/Symptoms adequately represent the RSV disease presentation in all age groups included in this study.

Medical Encounters

Treatment of RSV disease with rilematovir versus placebo may result in lower need for medical encounters; therefore, comparison will be done between intervention groups.

4.2.1. Study-specific Ethical Design Considerations

Potential participants' parent(s)/legally acceptable representative(s) will be fully informed of the risks and requirements of the study and, during the study, they 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 the participant would otherwise be entitled. Only participants whose parent(s)/legally acceptable representative(s) is/are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

Prior to signing the main consent form for the study, participant's parent(s) (preferably both if available or as per local requirements) or their legally acceptable representative(s) may specifically allow for the collection and testing of a nasal MT swab by signing the pre-screening (diagnostic) ICF. This is not required if a positive RSV diagnostic result based on a local SOC sample collected within 48 hours prior to anticipated randomization is available and used for determining study eligibility.

When referring to the signing of the ICF, the terms legal guardian(s) and legally acceptable representative(s) refer to the legally appointed guardian of the participant with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study (see Section 8) based upon the World Health Organization (WHO) recommendations for this age group.[23]

Investigational staff should take the customary measures to ensure that study-specific assessments such as blood sampling or nasal swabbing are performed with as little additional stress as possible for the participant. Investigators may use local anesthetics prior to blood sampling.

4.3. Justification for Dose

The pediatric exposure was targeted to be similar as the one observed in adults treated with 500 mg rilematovir qd and 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 the currently ongoing pediatric Study 53718678RSV2002, in which 2 dose levels were evaluated (5, 6, and 9 mg/kg as the high dose and 1/3rd of these doses as the low dose, qd), popPK analysis demonstrated that these high doses resulted in observed C_{min} and C_{max} values within the range of the target concentrations (ie, the exposure observed in adults treated with 500 mg rilematovir qd) for the different age groups (≥28 days to <3 months, ≥3 to <6 months, and ≥6 to <36 months of age). Furthermore, based on review of the safety and efficacy data from Studies 53718678RSV1005 and interim analysis of 53718678RSV2002, these proposed doses were generally safe and well tolerated and ensure the highest potential antiviral effect (see also Section 2.2). In addition, the efficacy data of Study 53718678RSV2002 indicate a more pronounced clinical effect at the high dose level of rilematovir compared to the low dose level whereas no dose-response was observed for safety outcomes.

Data from the mass-balance study (Study 53718678RSV1008) demonstrated that 8% of the parent was excreted in the feces, 1.2% of the parent was excreted in the urine, and 8% was excreted in the feces as the M8 metabolite (UGT pathway). Therefore, the popPK model has a combination of maturation functions that describe the increase in CYP3A4 and UGT1A3/1A4 with age, as fractions of their adult abundance and applied to total clearance. The popPK model has the same combination of maturation functions as well as allometric scaling applied to the other PK parameters.

Based on the exposure-response analysis conducted in the TQT Study 53718678RSV1009 in healthy adult participants, an exposure (C_{max}) related important potential risk of QT interval prolongation was identified. While no safety signal was observed regarding QT prolongation, other ECG abnormalities, or cardiovascular side effects, additional modeling to evaluate alternative dose and dosing regimens, which would allow to maintain the exposures (C_{trough}) at effective levels while reducing the C_{max}, to mitigate this potential risk was performed.

Based on final PK and QTc modeling, a 7-day bid dosing regimen of 2.5, 3, and 4.5 mg/kg for the 3 different age groups (≥28 days to <3 months, ≥3 to <6 months, and ≥6 to ≤5 years of age, respectively) was selected with disallowance of comedication with moderate or strong CYP3A4 inhibitors. Based on Table 4, the upper limit of the 90% confidence interval for ΔΔQTcI for the bid regimen for each of the age groups remains below 10 msec. It is anticipated that the proposed bid dosing will be in the therapeutic range of rilematovir for the pediatric population (C_{trough} at least 7 times $paEC_{90}$), ensuring the highest potential antiviral effect while minimizing the risk of

development of resistance, as well as mitigating the important potential risk of QT interval prolongation.

Table 4: Predicted Geometric Mean AUC_{24h}, C_{max}, C_{trough} and ΔΔQTcI Per Age Group After Day 1 and Day 7

Age Group (Dose mg/kg bid)	1 - <3 Months (2.5 mg/kg bid)	3 - <6 Months (3 mg/kg bid)	6 Months – 5 Years (4.5 mg/kg bid)
AUC_{24h} Day 1 (ng.hr/mL)	16,500	17,200	17,200
AUC_{24h} Day 7 (ng.hr/mL)	32,900	28,800	21,300
C_{max} Day 1 (ng/ml)	1,220	1,350	1,680
C_{max} Day 7 (ng/ml)	1,870	1,800	1,830
C_{trough} Day 1 (ng/mL)	566	509	287
C_{trough} Day 7 (ng/mL)	998	773	343
ΔΔQTcI Day 1 (msec) (90%CI)	1.95 (0.97-3.66)	2.09 (1.08-3.98)	2.35 (1.18-4.61)
ΔΔQTcI Day 7 (msec) (90%CI)	3.17 (1.34-6.81)	2.92 (1.31-6.23)	2.61 (1.25-5.45)

ΔΔ = placebo-adjusted change from baseline; AUC = area under the plasma concentration-time curve; AUC_{24h} = AUC from administration to 24 hours; bid = twice daily; C_{max} = maximum plasma concentration; C_{trough} = predose plasma concentration; QTcI = individual-corrected QT interval.

The dose for neonates (Age group 4) will be determined based on the results of the substudy and depend on IDMC recommendation, but will not exceed the exposures simulated for the bid regimen in pediatric subjects ≥28 days to ≤5 years of age and observed for the 250 mg bid regimen in adults. Investigators and relevant health authorities, ethics committees, and institutional review boards (IRBs) will be informed in writing of the decision and the selected dosing regimen for neonates.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit (phone visit or 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 (s)he has completed dosing and has completed assessments at Day 35 (±3 days) of the follow-up phase.

5. STUDY POPULATION

Screening for eligible participants will be performed within 3 days of first RSV sign/symptom onset, such that participants are randomized within ≤3 days of RSV sign/symptom onset, and within 4 hours before administration of the study intervention. Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed.

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 of the following criteria to be enrolled in the study:

1. Criterion modified per Amendment 1

1.1 The participant is a boy or girl either:

- Born at term (ie, after ≥37 weeks of gestation) and ≥28 days old to ≤5 years old at the time of consent.
- Born preterm (ie, at <37 weeks of gestation) and ≥28 days old corrected for gestational age and up to ≤5 years old at the time of consent.

Note: After this main study opens to neonate enrollment: in addition, a neonate (boy or girl) from birth at term (ie, after at least 37 weeks of gestation) to <28 days at the time of consent.

2. The participant weighs within ≥2.4 kg and ≤24.6 kg.

3. Each participant's parent(s) (preferably both if available or as per local requirements) or their legally acceptable representative(s) has/have signed an ICF indicating that (s)he:
   - understands the purpose of, and procedures required for, the study,
   - is willing for their child to participate in the study,
   - is willing for their child to remain in the hospital until at least Day 2,
   - is willing and able to adhere to the prohibitions and restrictions with regards to
     - the concomitant medication (see Section 6.8),
     - the lifestyle consideration (see Section 5.3),
     - study procedures and assessments to be performed by the parent(s)/caregiver(s) as well as those by the investigator/study site personnel.

   Note: Prior to signing the main consent form for the study, participant's parent(s) (preferably both if available or as per local requirements) or their legally acceptable representative(s) may specifically allow for the collection and testing of nasal MT swab by signing the pre-screening (diagnostic) ICF.

4. The participant has been diagnosed with RSV infection using a polymerase chain reaction (PCR)- or other molecular-based diagnostic assay.
Note: If a participant had a positive RSV test result using a molecular-based diagnostic assay from another study for which (s)he was otherwise ineligible or from a SOC molecular-based diagnostic test within 24 hours prior to start of screening and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for determination of eligibility.

5. Criterion modified per Amendment 1

5.1 The participant has an acute respiratory illness with at least 1 of the signs/symptoms listed in each of the following categories within 24 hours prior to start of screening and at screening, as evaluated by the investigator:

- **Upper respiratory tract infection:** nasal congestion or rhinorrhea; AND
- **Lower respiratory tract infection:** increased respiratory effort (as evidenced by subcostal, intercostal or tracheosternal retractions, grunting, head bobbing, nasal flaring, or tachypnea), wheezing[a], cough[a], cyanosis, or apnea; AND
- **Systemic/general:** feeding difficulties (defined as <75% intake of normal food amounts); dehydration; fever; disturbed sleep, or disturbed activity level (irritable/restless/agitated/less responsive).

[a] Cough or wheezing cannot be the only LRTI sign/symptom present, ie, at least one other LRTI sign/symptom needs to be present for eligibility.

6. The time of onset of RSV signs/symptoms to the anticipated time of randomization must be ≤3 days. Onset of signs/symptoms is defined as the time of the day (or part of the day if time of the day cannot be specified) the parent(s)/caregiver(s) became aware of the first sign and/or symptom consistent with respiratory or systemic/general manifestation of signs/symptoms of RSV infection. The time of sign/symptom onset has to be assessed as accurately as possible.

7. The participant is hospitalized or presented to the ER/clinic and expected to be hospitalized.

Note: Hospitalized refers to having at least 24 hours with an overnight stay in the hospital.

8. Participants are otherwise healthy or have (a) risk factor(s) for severe RSV disease (as listed in Table 2). Participants who are immunocompromised are excluded.

9. Except for the RSV-related illness, the participant must be medically stable based on physical examination, medical history, and vital signs performed at screening. If there are abnormalities, they must be consistent with the underlying condition (RSV disease and/or present risk factor[s] for severe RSV disease [refer to inclusion criterion #8] 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.

10. The participant must have been assessed per local public health practice and considered not to have SARS-CoV-2 infection during this respiratory infection.

5.2. Exclusion Criteria

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

1. The participant had major surgery within the 28 days prior to randomization or planned major surgery through the course of the study (eg, bidirectional Glenn procedure).

2. The participant has a neuromuscular disease that affects swallowing or the thoracic muscles, an evolving developmental disorder, major congenital anomalies or known cytogenetic or metabolic disorders other than the ones allowed above (see inclusion criterion #8).

   Note: Isolated open ductus arteriosus and open foramen ovale are not exclusionary as these are not considered major anomalies.

3. The participant is considered by the investigator to be immunocompromised, whether due to underlying medical condition (eg, known human immunodeficiency virus [HIV] infection, malignancy or genetic disorder other than immunoglobulin A deficiency) or medical therapy (eg, immunomodulators other than corticosteroids for the treatment of comorbidities, chemotherapy, radiation, stem cell or solid organ transplant).

4. The participant has a known or clinically suspected acute or chronically active hepatitis B or C infection (based on participant's medical history or on participant's examination) or history of active maternal hepatitis B or C infection around birth, unless the participant has tested negative for hepatitis B and C infection.

5. 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.

6. The participant is being treated with extracorporeal membrane oxygenation.

7. The participant is receiving chronic (home) oxygen therapy (ie, is dependent on oxygen) at the time of screening.

8. The participant is using any disallowed medication as listed in Section 6.8.

9. Participant whose mother received an investigational RSV vaccination during the pregnancy for this child and whose age is <3 months at time of screening.

10. The participant has known allergies, hypersensitivity, or intolerance to rilematovir or to any of the excipients of the rilematovir or placebo formulation (refer to the IB).[26]

11. The participant is currently participating or planned to participate in another clinical interventional study, during their participation in this study.

12. The participant has any physical abnormality which limits the ability to collect regular nasal specimens.

13. The participant is unable to take medications orally or has 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. Confirmed QTcF interval >450 msec per the machine read parameter result at screening. Presence of an abnormal QTcF interval should be confirmed by repeat ECG recording during screening.

15. Known personal or family history of Long QT Syndrome or sudden cardiac death.

16. Presence of repetitive ventricular premature contractions (>10/min), second or third degree heart block, or complete or incomplete left bundle branch block, or complete right bundle branch block per the machine read ECG result at screening. Presence of any of the above abnormalities should be confirmed by repeat ECG recording during screening.

17. Other clinically significant abnormal ECG findings not consistent with the present risk factor for severe RSV disease (if applicable) in the study population, as judged by the investigator based on the machine read ECG results at screening.

***NOTE*:** Investigators should ensure that all study enrollment criteria have been met before the start of treatment. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after diagnosis/randomization but before the first dose of study intervention is given such that (s)he no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3.

5.3. Lifestyle Considerations

The parent(s)/caregiver(s) should complete the ObsRO Signs/Symptoms and ObsRO GHQ twice daily on an electronic device until Day 14, and once daily from Day 15 to Day 21 and the Caregiver Impact Questions daily until Day 21, which takes approximately 5-10 minutes per assessment, depending on the signs/symptoms. The parent(s)/caregiver(s) is/are required to perform all site visits per the Schedule of Activities.

Participant's parent(s)/caregiver(s) must be willing and able to adhere to the prohibitions and restrictions with regards to the concomitant therapy during the course of the study for the participant to be eligible for participation. Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study.

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 (ARI) episode in case RSV(-) diagnosis was the reason for screen failure.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Eligible participants will be randomized 2:1 (active:placebo) to receive either rilematovir or placebo bid for 7 days (14 consecutive doses). Study intervention administration should start as soon as possible, but within 4 hours after randomization.

Description of Interventions

Arm Name	Arm 1	Arm 2
Intervention Name	**Rilematovir**	**Placebo**
Type	Drug	Drug
Dose Formulation	Powder and solvent for oral suspension	Powder and solvent for oral suspension
Unit Dose Strength(s)	eq. 20 mg/mL[a]	Matching placebo
Dosage Level(s)	Doses are based on body weight and age group, see Table 5	
Route of Administration	Orally using a dosing syringe, during hospitalization may also be administered through nasogastric tube, if already in place.	
Use	Experimental	Placebo
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	Each unit will be labeled with unique medication ID number	
	The powder and solvent for oral suspension are packaged in amber glass bottles with child resistant closure.	
	Labels will contain information to meet the applicable regulatory requirements.	
Food/Fasting requirement	Regardless of food intake	
Other requirements	Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM).	
[a] After reconstitution, rilematovir is dosed as an equivalent 20 mg/mL JNJ-53718678-AAA oral suspension (containing 23 mg/mL JNJ-53718678-ZCL, the hemi-tartrate of JNJ-53718678-AAA).		

Table 5: Treatment Overview

Treatment	Age Group	Age Range	Dosing Regimen[a]	Volume Oral Suspension[b]
Rilematovir	1	≥28 days to <3 months	2.5 mg/kg bid on Days 1 to 7(/8)	A mL
	2	≥3 to <6 months	3 mg/kg bid on Days 1 to 7(/8)	B mL
	3	≥6 months to ≤5 years	4.5 mg/kg bid on Days 1 to 7(/8)	C mL
	4*	birth at term to <28 days	X[c] mg/kg bid on Days 1 to 7(/8)	D[c] mL
Placebo	1,2,3, or 4*	see above	Matching placebo bid on Days 1 to 7(/8)	A, B, C, or D[c]* (respectively) mL placebo

bid = twice daily; IDMC = Independent Data Monitoring Committee; IWRS = interactive web response system.
* After opening of recruitment in neonates in the main study dependent on positive IDMC recommendation after completion of a substudy in neonates (see Section 9.6).

a. Doses are provided for JNJ-53718678-AAA.

b. A to D represents the volume of oral rilematovir suspension to obtain the required dose of JNJ-53718678-AAA or the volume of the matching placebo suspension. After reconstitution, rilematovir is dosed as an equivalent 20 mg/mL JNJ-53718678-AAA oral suspension (containing 23 mg/mL JNJ-53718678-ZCL, the hemi-tartrate of JNJ-53718678-AAA), to be used depending on the bodyweight of the participant. The required volume to be administered per intake will be calculated by the IWRS and provided to the sites.

c. Dose dependent on outcome of the substudy in neonates and following IDMC review and recommendation. The dosing regimen will not exceed the exposures simulated for the bid regimen in pediatric subjects ≥28 days to ≤5 years of age and observed for the 250 mg bid regimen in adults.

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. Dosing should occur approximately every 12 hours. Administration of the second dose may be delayed or brought forward (by maximum 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 rilematovir or placebo PM of Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all participants receive 14 consecutive doses in total.

During hospitalization: the study intervention will be administered by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel.

After discharge: the study intervention will continue to be administered at home by the parent(s)/caregiver(s) through Day 7 (or Day 8 AM if first dose is given PM on Day 1). Study site personnel will instruct each participants' parent(s)/caregiver(s) on how to administer and store study intervention for at-home use as indicated for this protocol.

Study site personnel will record the bid study intervention administration in the source documents (during hospitalization) and in the eCRF (all doses).

If the participant vomited, regurgitated, or did not completely swallow the study intervention, the participant should not be redosed for that administration timepoint.

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 has elapsed, the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dosing schedule.

If a participant is rehospitalized after discharge due to worsening of RSV disease during the treatment period, administration of study intervention in the bid regimen should continue.

If a participant's level of care during hospitalization changes during the treatment period, administration of study intervention in the bid regimen should continue.

The drug product is supplied as an eq. 217.4 mg/g JNJ-53718678-AAA powder (containing 250 mg/g JNJ-53718678-ZCL, the hemi-tartrate of JNJ-53718678-AAA) or placebo and solvent for oral suspension. The powder needs to be reconstituted with an appropriate volume of solvent for oral suspension to obtain an eq. 20 mg/mL JNJ-53718678-AAA (containing 23-mg/mL JNJ-53718678-ZCL, the hemi-tartrate of JNJ-53718678-AAA) or placebo oral suspension by appropriately trained study site personnel prior to administration/dispensing to the participant's parent/caregiver.

Depending on the body weight and age of the participant, the IWRS will assign the appropriate number of bottles to be prepared and dispensed to the parent/caregiver.

Study intervention will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[26]

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/study site investigational product and procedures manual for additional guidance on study intervention preparation, 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.

During hospitalization, the study intervention administered to the participant must be documented on the intervention accountability form. 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. After discharge, the dispensing of study intervention to the participants' parent(s)/caregiver(s), and the return of study intervention from the participants' parent(s)/caregiver(s) (if applicable), must be documented on the intervention accountability form. Participants' parent(s)/caregiver(s) must be instructed to return the original container, whether empty or containing study intervention.

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 participants' parent(s)/caregiver(s), 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.

Potentially hazardous materials containing hazardous liquids, ie, oral dosing syringes, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

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 parent(s)/caregiver(s) of 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 will be provided.

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 the 2 treatment groups (rilematovir or placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by presence of risk factors for severe RSV disease (otherwise healthy vs presence of [a] risk factor[s] for severe RSV disease) and by region. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit(s) 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 treatment 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, time, and reason for the unblinding must be documented by the IWRS and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

For participants who have had their intervention assignment unblinded, study intervention must be discontinued (see Section 7.1).

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

Dosing should occur approximately every 12 hours, while hospitalized, by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel and after discharge by the parent(s)/caregiver(s).

At the screening visit, the participant's parent(s)/caregiver(s) will receive instructions on compliance with and documentation of study intervention administration, and this instruction will be repeated at the time of discharge, if applicable. During the course of the study, the investigator or designated study site personnel will be responsible for providing additional instruction to re-educate any participant's parent(s)/caregiver(s) who is (are) not compliant with administering the study intervention and recording date, time, and any issues encountered during dosing.

6.5. Dose Modification

Dose modification is not allowed within this study.

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

Participants' parent(s)/caregiver(s) 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 the study intervention greater than the total daily calculated volume for the respective age and body weight-based dose within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific intervention 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 for at least 3 days.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Concomitant medications, except those listed below, are allowed during this study. All concomitant medications and supportive therapy (including but not limited to prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements, and non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, physiotherapy) different from the study intervention must be recorded in the eCRF, from the date

the ICF for the study is signed through the end-of-study visit. Recorded information will include a description of the type of the drug/therapy, treatment duration (dates of treatment start and stop), dose regimen, route of administration, and its indication. Modification of an effective pre-existing chronic 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.

All hospitalized participants will receive supportive care per local institution standards and applicable guidelines. While treatment guidelines and standards vary based on local practice and are guiding the management of participants, within the parameters of this study, it is recommended that supplemental oxygen can be administered or withdrawn, as appropriate, to maintain an SpO_2 ≥92% as long as it is medically indicated (for participants whose SpO_2 is ≥92% when clinically stable). It is further recommended that re-initiation of oral hydration and feeding occur as soon as possible. Refer to Section 10.9, Appendix 9 for guidelines on performing SpO_2 measurements.

In addition, it is recommended to limit the use of antitussives and mucolytics, following their package insert and clinical practice guidelines, in particular in the younger age group.

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.

In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics.

Fexofenadine is allowed, taking into account its package insert and dosing instructions for use in children, but rilematovir may reduce the fexofenadine exposure by 65% and reduce its efficacy if administered simultaneously. To limit the reduction in efficacy it is recommended to administer fexofenadine at least 1 to 2 hours before taking study intervention and/or at least 4 hours after taking study intervention, taking into account the local prescribing information for fexofenadine.

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

- inhaled β-agonists or anticholinergics
- oral/IV/intramuscular antibiotics such as β-lactams (see below for antibiotics which are CYP3A4 inhibitors)

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.

Routine vaccinations are permitted during the study but their package inserts and/or local clinical practice guidelines have to be followed. In case COVID-19 vaccines are locally approved

(including emergency use authorized) in the pediatric population, please refer to Section 10.19, Appendix 19 for guidance.

Disallowed Medications

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

- Prescription medication eltrombopag, a known BCRP inhibitor, within 2 days prior to randomization and during the study.
- Herbal supplements with active metabolic enzyme inducing components (eg, St-John's Wort) within 21 days or BCRP (a transporter protein) inhibiting components (eg, curcumin) within 2 days prior to screening and during the study except for topically administered products.
- Systemic corticosteroids if used for >7 consecutive days immediately prior to screening at doses higher than 2 mg/kg/day of prednisone or equivalent. Participants meeting the eligibility criteria at screening but requiring initiation or increased doses of systemic corticosteroids (>2 mg/kg/day of prednisone or equivalent) for a prolonged period (>7 consecutive days) during the study are allowed to continue participation in the study.
- Medications with a known risk to prolong the QT interval[24] and not belonging to the class of moderate or strong CYP3A4 inhibitors (eg, azithromycin, a mild CYP3A4 inhibitor with known QT prolonging risk) 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.
- The following prescription medications within 14 days prior to screening and during the study:

  Prescription medications which are known to be a moderate or strong inhibitor of CYP3A4 enzymes, such as, but not limited to, macrolide antibiotics.

  Prescription medications that are known to be strong inducers of CYP3A4 such as, but not limited to, rifampin.

  Prescription medications intended to prevent or treat the RSV infection itself (eg, ribavirin, IV immunoglobulin). Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted.
- Palivizumab, within 5 half-lives prior to screening and during the study.
- Any other investigational study intervention within 30 days or 5-fold half-lives of that drug (whichever is longer) prior to screening and during the study.
- Prior exposure to rilematovir at the time of screening.
- Any investigational medical device prior to screening.
- Any investigational RSV vaccine at any time prior to and during the study. Routine vaccinations are permitted during the study but their package inserts and local clinical practice guidelines have to be followed.

- Maternal vaccination with an investigational RSV vaccine during the pregnancy for this child and whose age is <3 months at time of screening (Section 5.2, Exclusion Criteria).

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

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's parent(s)/caregiver(s) withdraw(s) consent to receive study intervention.
- The investigator considers that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant experiences a Grade 3 rash or higher.
- The participant is reported with a laboratory abnormality of ALT increase ≥3 × upper limit of normal (ULN) in the screening sample and met the liver chemistry stopping criteria, refer to Sections 8.3.5.1 and 10.8, Appendix 8.
- The participant has a confirmed QTcF interval ≥500 msec based on a machine read ECG result (see also Section 8.3.5.2). Confirmation needs to be obtained during the same visit day by repeat ECG recording.
- The participant is reported with any other laboratory abnormality of Grade 3 or 4 at screening, confirmed in a repeat test (centrally), to be performed within 48 hours of the result being available at the site.
- The participant's parent(s)/caregiver(s) is/are poorly compliant with completing ObsRO Signs/Symptoms and ObsRO GHQ questionnaires, preferably after evaluation and discussion between the investigator and the sponsor.
- The participant's parent(s)/caregiver(s) is/are poorly compliant with other study procedures, visits, and assessments, 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.

In case a participant prematurely discontinues study intervention for any reason, refer to the Schedule of Activities for the required visits and assessments to be performed.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

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's parent(s)/caregiver(s) is poorly compliant with study procedures, visits, and assessments, preferably after evaluation and discussion between the investigator and the sponsor
- Decision by the sponsor to stop or cancel the study
- Decision by the investigator to withdraw the participant from the study
- Decision by local regulatory authorities and Independent Ethics Committee (IEC)/IRB to stop or cancel the study.

In case the participant prematurely discontinues study participation, refer to the Schedule of Activities for the required visits and assessments to be performed.

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

Withdrawal of Consent

When a participant's parent(s)/caregiver(s) withdraw(s) the participant before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason is withdrawal of consent for further study participation, then no additional assessments are allowed. However, an optional Follow-up Visit will be offered to safeguard the participant in such case the participant's legally acceptable representative(s) withdraw(s) consent from the study.

A participant's parent(s)/caregiver(s) declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant's parent(s)/caregiver(s) agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Samples in Future Research

The participant's parent(s)/caregiver(s) may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 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

A participant will be considered lost to follow-up if the participant's parent(s)/caregiver(s) repeatedly fail(s) to return with the participant for scheduled visits and is (are) 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's parent(s)/caregiver(s) are deemed futile. The following actions must be taken if a participant's parent(s)/caregiver(s) fails to return with the participant to the study site for a required study visit:

- The study site personnel must attempt to contact the participant's parent(s)/caregiver(s) to reschedule the missed visit as soon as possible, to counsel the participant's parent(s)/caregiver(s) on the importance of continuing regular visits and assessments until the end of the study (ie, visit Day 35), to ascertain whether the participant's parent(s)/caregiver(s) wish(es) to or should continue to have the participant 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's parent(s)/caregiver(s) (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's parent(s)/caregiver(s)'s last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant's parent(s)/caregiver(s) 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's parent(s)/caregiver(s) 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 all measurements applicable to this study. Unscheduled visits may be performed based on the investigator's clinical judgment and may include further evaluations, as needed. In addition, the study site personnel may contact the parent(s)/caregiver(s) by phone (or other means of contact as agreed upon) after the daily review of the ObsRO GHQ up to Day 21.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: non-invasive procedures should be collected first before invasive procedures (ECG, then vital signs/SpO_2, then nasal MT swab, and blood draw last). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions assessments should preferentially be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant's parent(s)/caregiver(s) responses, with the exception of the screening assessment, which can take place after clinician assessment of eligibility.

Clinical course and severity of RSV infection will be assessed through different measures (see Section 8.1.1).

The need for supplemental oxygen and supplemental feeding/hydration will be assessed throughout the study. Refer to Section 8.1.1.1 for the definition of need for supplemental oxygen/feeding/hydration.

ClinRO and ObsRO Signs/Symptoms will be used to monitor signs/symptoms of RSV disease, ClinRO and ObsRO GHQs will be used to monitor its evolution over time, and Caregiver Impact Questions will be used to monitor parent(s)/caregiver(s) quality of life as described in Section 8.1.1.3.

All parental study-related assessments will ideally be performed by the same parent (or caregiver) throughout the study, if feasible.

Assessment of antiviral activity and viral sequencing will be performed as described in Sections 8.1.2 and 8.1.3, respectively.

Safety and tolerability, including AEs, laboratory assessments, ECGs, vital signs, and physical examination will be assessed throughout the study from signing of the ICF until the participant's last study-related activity (see Sections 8.2 and 8.3). Refer to Section 10.9, Appendix 9 for guidelines on performing vital signs and SpO_2 measurements.

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

Medical encounter data will be collected. Refer to Section 8.6 for details.

Acceptability and palatability will be assessed (see Section 8.7).

Residual blood samples and leftover nasal MT swab samples from samples collected during the study may be used for exploratory biomarker analyses (see Section 8.8).

The presence of other respiratory viruses or bacteria will be assessed as described in Section 8.9.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the 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 per the Schedule of Activities will not exceed 9.2 mL plus 80 µL for PK samples over the duration of the study and is in line with recommendations collated by the WHO.[23] Repeat tests (see Section 8.2.4) could increase the total blood volume.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Nasal Sample Collection and Handling

For the evaluation of antiviral activity, the RSV viral load in nasal MT swabs will be measured at the central laboratory using a qRT-PCR assay (see Section 8.1.2, Antiviral Activity). Viral sequencing will also be performed on the nasal MT swabs (see Section 8.1.3). Only nasal MT 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 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.

The presence of viral (other than RSV) or bacterial co-pathogens will be assessed in the nasal MT swab sample by using PCR at the central laboratory (see Section 8.9).

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 IB and any addenda
- Pharmacy manual/study site investigational product and procedures manual, and oral dosing syringes
- Laboratory manual and specimen collection materials
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- eDevice and instructions for use
- Contact information page(s)
- ECG machine and manual

- Additional auxiliary materials, as needed

The participant's parent(s)/caregiver(s) will be provided with tools to facilitate/support participation, such as:

- eDevice and instructions for use
- Study information and instruction sheets for parent(s)/caregivers(s) regarding study visits and procedures, eg, dosing, ObsRO Signs/Symptoms, ObsRO GHQ, Caregiver Impact Questions, and Acceptability and Tolerability Assessment
- Oral dosing syringes

8.1. Efficacy Assessments

8.1.1. Clinical Severity and Clinical Course of RSV Infection

8.1.1.1. RSV Recovery Scale Assessments

The RRS is an ordinal scale assessing a participant's clinical status as defined per protocol. The study day on which the RRS will be assessed as the primary endpoint is the first study day when at least 50% of the participants across treatment arms are discharged from the hospital (with or without signs/symptoms). This study day will be determined in a blinded manner based on all available data irrespective of the treatment group at the time of the first interim analysis and by an independent statistician in order to protect data integrity. This study day will be used for any further interim analysis as well as for the final analysis. The RRS will also be assessed on Days 2 to 8 (excluding the primary time point) as secondary endpoints.

The RRS provides 7 mutually exclusive conditions ordered from best to worst, and the analysis score reflects the participant's worst situation on the study day of assessment:

1. Not Hospitalized Without Signs/Symptoms*

2. Not Hospitalized With Signs/Symptoms*

3. Non-ICU Hospitalization, Not Requiring Supplemental Oxygen NOR Supplemental Feeding/Hydration

4. Non-ICU Hospitalization, Requiring Supplemental Oxygen AND/OR Supplemental Feeding/Hydration

5. Admitted to the ICU, Not Requiring Mechanical Ventilation**

6. Requiring Mechanical Ventilation**

7. Death

*With or without signs/symptoms is defined by the Key RSV Signs/Symptoms of ObsRO Signs/Symptoms as being not resolved or resolved (absent or mild), respectively (see Section 10.14, Appendix 14).
**Mechanical ventilation includes both invasive and non-invasive mechanical ventilation.

The RRS categories are defined below and are referred to as protocol-defined categories, ie, the categories to which the participant should be assigned based on the data reported in the eCRF and eCOA, rather than the category where (s)he may actually be. This might result in a categorization of the participant in a worse or better category than where (s)he actually is.

RSV Recovery Scale: Definitions

Note: For purposes of this protocol, discharge readiness refers to a participant having:

improved respiratory effort (eg, improved retractions, stable respiratory rate)

improved O_2 saturation to ≥ 92% without need for supplemental oxygen

fever control

adequate hydration/feeding without supplementation

stable and/or baseline mental status

1. Not hospitalized without signs/symptoms

Participant met either of the 2 following criteria:

Discharged from the hospital before the day of assessment.

Hospitalized at the day of assessment but ready for discharge on both the day of assessment and the day prior, as judged by the investigator.

Without signs/symptoms is defined by:

Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms (see Section 10.11, Appendix 11) resolved (absent or mild) on the day of assessment (see Section 10.14, Appendix 14).

2. Not hospitalized with signs/symptoms

Participant met either of the 2 following criteria:

Discharged from the hospital before the day of assessment.

Hospitalized at the day of assessment but ready for discharge on both the day of assessment and the day prior, as judged by the investigator.

With signs/symptoms is defined by:

Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms (see Section 10.11, Appendix 11) not resolved on the day of assessment (see Section 10.14, Appendix 14).

3. Non-ICU hospitalization, not requiring supplemental oxygen NOR supplemental feeding/hydration

Participant met either of the 2 following criteria:

Non-ICU hospitalized on the day of assessment (including readmittance) and neither supplemental oxygen nor supplemental feeding/hydration is required by the participant and not ready for discharge during the whole day of assessment, as judged by the investigator.

In the ICU but there is no medical reason to be in the ICU during the day of assessment and neither supplemental oxygen nor supplemental feeding/hydration is required by the participant and not ready for discharge during the whole day of assessment, as judged by the investigator.

4. Non-ICU hospitalization, requiring supplemental oxygen AND/OR supplemental feeding/hydration

Participant met either of the 2 following criteria:

Non-ICU hospitalized on the day of assessment (including readmittance) and either supplemental oxygen or supplemental feeding/hydration or both is/are required by the participant.

In the ICU but there is no medical reason to be in the ICU during the day of assessment, and either supplemental oxygen or supplemental feeding/hydration or both is/are required by the participant.

Requiring oxygen supplementation is defined by:

Having an SpO_2 <90% while receiving supplemental oxygen.

Receiving supplemental oxygen (and having an SpO_2 ≥90%) through a face mask or nasal cannula and not being able to sustain an SpO_2 of ≥92% when breathing room air for 10-15 minutes at any time on the day of assessment (Refer to Section 10.9, Appendix 9 for guidelines on performing the measurement).

Not receiving supplemental oxygen and either:

- Having an SpO_2 of <92% at any measurement on the day of assessment, or
- In case of known pre-RSV SpO_2 <92% (eg, due to pulmonary dysplasia), the current SpO_2 on room air is lower than pre-RSV infection levels by at least 3%.

Requiring supplemental feeding/hydration by IV administration and/or nasogastric tube on the day of assessment is defined by:

Oral intake is <50% of normal.

5. Admitted to the ICU, not requiring mechanical ventilation

Participant met either of the 2 following criteria:

In the ICU (and ICU level of care is required at any time during the day of assessment).

On the hospital ward, but deemed to require ICU level of care at any time during the day of assessment (eg, not transferred to ICU due to bed availability), irrespective of supplemental oxygen/feeding.

Requiring ICU level of care is defined by:

Some specific conditions:

- Treatment of acute unstable arrhythmias
- Treatment of complicated acid-base or electrolyte imbalances

- Utilization of IV vasoactive medications
- Status post cardiac arrest
- Cardiogenic Shock
- Acute congestive heart failure
- Acute or imminent respiratory failure
- Hemodynamic instability
- High supplemental oxygen requirement (fraction of inspired oxygen [FiO_2] ≥50%)
- Requirement for more frequent or continuous inhaled or nebulized medications than cannot be administered safely on general pediatric ward.

Other conditions requiring specialized equipment and/or staff competencies only available in the ICU and not due solely to pre-existing conditions or prematurity unless due to worsening of that condition.

6. Requiring mechanical ventilation

Any oxygen support requiring intubation or extracorporeal oxygenation.

Mechanical ventilation (invasive [oxygen supplementation requiring intubation or extracorporeal oxygenation] or non-invasive [a) Positive-pressure ventilation such as continuous positive airway pressure (CPAP), positive end-expiratory pressure (PEEP) ventilation, b) Negative-pressure ventilation such as continuous negative extra-thoracic pressure (CNEP), continuous negative pressure (CNP)]) is used at any time on the day of assessment.

7. Death

Participant died at any time on the day of assessment or earlier (all-cause mortality).

8.1.1.2. Other Clinical Course and Clinical Severity Assessments

The study will include the following additional evaluations of the clinical course of RSV disease:

- Clinical resolution from RSV disease as assessed daily from Day 2 to Day 8, and defined by:
  - Free of oxygen supplementation, AND
  - Free of supplemental feeding, AND
  - Not requiring ICU (as defined in Section 8.1.1.1), AND
  - Key RSV Signs/Symptoms resolved to absent or mild as per the ClinRO Signs/Symptoms (see Section 8.1.1.3).
- Evolution and severity of signs/symptoms of RSV disease as assessed by the parent(s)/caregiver(s) (ObsRO Signs/Symptoms) and by the investigator (ClinRO Signs/Symptoms) on an electronic device (see Section 8.1.1.3).
- Evolution of the RSV disease based on ObsRO GHQ and ClinRO GHQ as assessed by the parent(s)/caregiver(s) and by the investigator, respectively, on an electronic device.

- Oxygen supplementation requirement type (invasive mechanical, non-invasive mechanical, and non-invasive non-mechanical), and duration.
- Hydration and feeding by IV line/nasogastric tube and duration.
- The occurrence of the following RSV-disease related complications, with onset after treatment initiation (see Section 10.18, Appendix 18 for definitions), as reported by the investigator as AE based on the available clinical information (see also Section 8.3):
    - Respiratory complications: respiratory failure, apnoeic attacks, bronchiolitis/bronchial obstruction, pneumonia, asthmatic crisis;
    - Infectious complications: otitis media, bacterial respiratory tract infections, sepsis;
    - Cardiovascular complications: arrhythmia, cardiogenic shock, hemodynamic instability, congestive cardiac failure;
    - Acid-base or electrolyte complications, based on laboratory values if considered clinically relevant:
        - metabolic acidosis (serum HCO_3 <16),
        - metabolic alkalosis (serum HCO_3 >30),
        - hyponatremia (Na^+ <130 mEq/L),
        - hypokalemia (K^+ <2.9 mEq/L),
        - hyperkalemia (K^+ >6.0 mEq/L),
        - hypocalcemia (Ca^{2+} <7.7 mg/dL or equivalent to Grade 2 in children ≤3 months of age),
        - hypercalcemia (Ca^{2+} >11.9 mg/dL or equivalent to Grade 2 in children ≤3 months of age),
        - hypoglycemia (glucose <54 mg/dL),
        - hyperglycemia (glucose >160 mg/dL).
- Clinical parameters: respiratory rate, heart/pulse rate, SpO_2, and body temperature as measured by the investigator during scheduled visits. Refer to Section 10.9, Appendix 9 for guidelines on performing these assessments.
- Time to first hospital discharge (from start of dosing).
- Time to readiness for hospital discharge.
- Reason for hospital discharge or for no discharge despite being clinically ready for discharge (as defined in Section 8.1.1.1).
- The requirement for transition to ICU and duration of ICU stay.
- Proportion of participants requiring rehospitalization for respiratory/other reasons.
- Number and type of medical encounters (see also Section 8.6).
- Incidence of antibiotic treatment episodes.
- Incidence of systemic or inhaled corticosteroids and bronchodilators use.

- Impact of child's RSV disease on the parent(s)/caregiver(s) and family as assessed by the Caregiver Impact Questions (see Section 8.1.1.3).

The pre-enrollment status of the participant will be captured based on the clinical assessments performed at presentation to the hospital (based on source documents) or prior to enrollment.

8.1.1.3. ClinRO and ObsRO Clinical Outcome Assessments and Caregiver Impact Questions

The PRESORS developed by the sponsor to monitor RSV severity and its impact in pediatric patients include several assessments that the clinicians treating the study participants and the parents/caregivers of participants need to complete on an electronic device at the timepoints specified in the Schedule of Activities. In case of a bid schedule for the PRESORS, assessments are expected to be performed approximately every 12 hours. Every effort should be made to have at least 8 hours between assessments. The PRESORS for the clinicians consists of the ClinRO Signs/Symptoms, the ClinRO GHQ, and an additional question regarding apnea (see Section 10.13, Appendix 13). The PRESORS for the parents/caregivers (PRESORS ObsRO) consist of ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Information (only assessed during set up of the electronic device) (see Section 10.10, Appendix 10, Section 10.11, Appendix 11, and Section 10.12, Appendix 12). The sponsor developed the ClinRO and ObsRO Signs/Symptoms assessments to monitor signs/symptoms of RSV disease severity observed and rated by clinicians treating pediatric participants as well as by the participant's parent(s)/caregiver(s) from baseline through end of follow-up. Clinicians and parent(s)/caregiver(s) are instructed to rate each sign/symptom at its worst during the recall period. The ClinRO and ObsRO GHQs provide assessments by the clinicians and the parent(s)/caregiver(s), respectively, of the overall impression of the participant's RSV disease severity, change in the participant's RSV disease, and overall health status. In addition to the ObsRO Signs/Symptoms and ObsRO GHQ, parents/caregivers will also be asked to complete Caregiver Impact Questions (see Section 10.12, Appendix 12) and an assessment of acceptability and palatability (see Section 8.7 and Section 10.16, Appendix 16) at the timepoints specified in the Schedule of Activities on the same electronic device.

"Resolution of Key RSV Signs/Symptoms" used in several endpoints refers to the Key RSV Signs/Symptoms assessed by the ClinRO Signs/Symptoms or ObsRO Signs/Symptoms, as specified, as being resolved (absent or mild) or not resolved (see Section 10.14, Appendix 14, and Section 10.15, Appendix 15 for definitions of resolved/not resolved). The Key RSV Signs/Symptoms are:

- Breathing Problems
- Retractions
- Tachypnea
- Cough
- Wheezing (ClinRO) / Breathing Sounds (ObsRO)
- Tachycardia

Additional general illness and upper respiratory tract signs/symptoms of RSV disease assessed by the ClinRO Signs/Symptoms and/or ObsRO Signs/Symptoms are listed below. Refer to Section 10.14, Appendix 14, and Section 10.15, Appendix 15 for definitions of resolved/not resolved.

- Activity Level (ClinRO) / General Illness Behavior (ObsRO)
- Sleep Disturbance
- Crying (ObsRO only)
- Feeding Problems
- Dehydration
- Nasal Secretions (ClinRO) / Nasal Signs (ObsRO)

Signs/symptoms reported in these assessments will not be reported as AEs but constitute a part of the efficacy evaluations.

For completion of the ClinRO Signs/Symptoms, chest, nose, and head examination (including visual inspection and auscultation) needs to be performed.

The Caregiver Impact Questions assess how worried parent(s)/caregiver(s) was/were about his/her/their child's health and how much time impact the child's disease meant, including hours missed from work. The Caregiver Impact Questions are asked to be completed by parent(s)/caregiver(s) on an electronic device at the timepoints specified in the Schedule of Activities (see Section 10.12, Appendix 12). Responses to these questions are not mandatory, but provide valuable information about the impact of the child's illness and recovery on the child's family.

ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions will ideally be performed by the same parent/caregiver throughout the study, if feasible. If these assessments are performed during hospitalization or an on-site visit, they should preferentially be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant's parent(s)/caregiver(s) perceptions, with the exception of the screening assessment, which can take place after clinician assessment of eligibility.

The investigator/study staff will provide sufficient information (included in the study manual and caregiver study information packet) to enable the parent(s)/caregiver(s) to complete the assessments on the electronic device correctly and on schedule to avoid missing or incorrect data. Prior to completing the screening assessment, the parent(s)/caregiver(s) must complete a training module (included on the electronic device) on how to enter responses to questions on the electronic device. The parent(s)/caregiver(s) may also choose to complete the Caregiver Information, ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions on a personal device (web diary).

The Caregiver Information, ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions will be provided in the local language in accordance with local guidelines.

8.1.2. Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal MT swab samples 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. Nasal MT swab specimens for the determination of RSV viral load will be collected at several timepoints during the study as indicated in the Schedule of Activities and Figure 3. Date and time of sampling will be collected. Nasal MT swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). The nostril that was sampled will be documented by the study site personnel.

During screening, a study-specific screening sample (nasal MT swab) will be collected for the local diagnosis of RSV infection using a PCR or other molecular-based diagnostic assay. If the participant is subsequently randomized, the remaining sample content should be shipped for central testing of RSV viral load and viral sequencing. However, if an RSV positive diagnostic test result from a sample collected per local SOC testing within 24 hours prior to start of screening is available this may also be used to determine study eligibility. In such case, the collection of the study-specific screening nasal MT swab is not applicable.

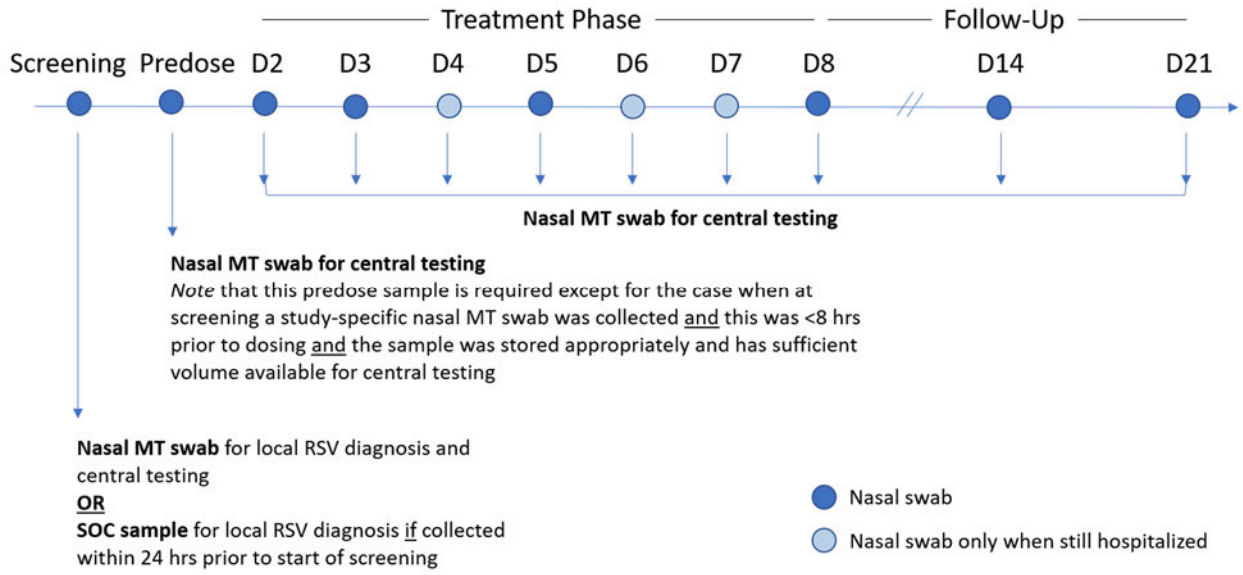
The predose nasal MT swab on Day 1 should be collected as close as possible prior to the first administration of study intervention. If a study-specific screening nasal MT swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline predose sample, provided that the study-specific screening nasal MT 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 whole remainder of the original sample is available). Only in such case, no additional sample needs to be collected at Day 1 predose. The next nasal swabs should be collected preferably at approximately the same time as the predose swab taken on Day 1 and preferably prior to dose administration of the next days.

The baseline predose nasal MT swab will be used for central confirmation of RSV diagnosis, determination of RSV viral load, viral sequencing and determination of the presence of other respiratory viruses or bacteria. These assessments will be performed on the leftover from the screening nasal MT swab sample in case that sample can be used as the predose sample (if collected within 8 hours prior to dosing and provided appropriate storage and sufficient volume available).

Throughout the treatment phase and follow-up phase the investigational staff will collect nasal MT swabs for determination of RSV viral load and viral sequencing (see Figure 3):

- During hospitalization: Swabs will continue to be collected each day during hospitalization through Day 8 and on Days 14 and 21 or until discharge (whichever comes first).
- Discharged participants: Swabs will be collected at each scheduled on-site (or home) visit through Day 21.

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



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

The collection of these nasal MT swabs and date and time of sampling should be recorded for all participants in the eCRF.

8.1.3. Viral Sequencing

Viral resistance will be monitored by sequencing of the RSV F gene in all baseline (predose or screening) nasal swab samples and in subsequent samples upon request of the sponsor's virologist. Other regions of the RSV genome may also be sequenced at discretion of the sponsor's virologist. Sequencing results will 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 Section 10.3, Appendix 3.

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

To evaluate the participant's eligibility, a complete physical examination of all body systems, including length or height, head circumference, and body weight measurements will be performed at screening.

A directed physical examination will be performed at several time points throughout the study. The directed physical examination is inclusive of the examination needed for the ClinRO Signs/Symptoms completion (see Section 8.1.1.3): respiratory system, nose and ear, as well as the throat and facial and neck lymph nodes. On Day 21, also length or height, head circumference, and body weight measurements will be included (see Schedule of Activities).

To obtain the actual body weight, participants are advised to be weighed unclothed with a dry diaper only or lightly clothed, with consistency for all visits. Length may be assessed in the supine position and the same position should be used for the subsequent assessments of that participant.

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 AE.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and SpO_2 will be assessed as part of the clinical parameters (Section 8.1.1.2).

Additional vital signs assessments include systolic blood pressure and diastolic blood pressure.

Refer to Section 10.9, Appendix 9 for guidelines on performing vital signs assessments.

For the duration of hospitalization, vital signs will be assessed for each participant twice daily preferably at approximately the same time on each scheduled day. After discharge, vital signs will be assessed once during the on-site visits. See Schedule of Activities.

Any clinically relevant abnormalities occurring during the study should be recorded in the AE Section of the eCRF.

8.2.3. Electrocardiograms

Screening and on-treatment ECGs will be collected at the time points indicated in the Schedule of Activities. Day 1 and Day 3 ECGs should be taken approximately one hour (45-90 minutes) after administration of study intervention.

The participant should be supine (infants can be lying on their parent's/caregiver's arm) and rested for at least 5 minutes and preferably sleeping or calm (ie, not crying).

Electrocardiograms (12-lead ECG) should be performed using procedures commensurate with the participant's age.

For eligibility determination, the machine read ECG results, printed on the ECG device print-out of the ECG tracing, will be taken into account. 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 generated by the central ECG laboratory: a preliminary report and a final report. Both ECG reports 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 occurring during the study should be recorded by the investigator in the AE Section of the eCRF.

In the event that an invasive procedure such as a blood draw or nasal swab and an ECG are required at approximately the same time, the ECG should be collected first. Electrocardiograms may be repeated at the investigator discretion.

The investigator will be responsible for evaluating the results and determining if any findings are of clinical significance. If a participant has a QTcF interval ≥500 msec based on the machine read ECG results, confirmation needs to be obtained during the same visit day by repeat ECG recording. If confirmed, the participant needs to be withdrawn from study intervention (see also Section 7.1). In case 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 random urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. If a participant has a laboratory abnormality of ALT increase ≥3 × ULN in the screening sample and met the liver chemistry stopping criteria (see Section 10.8, Appendix 8), the participant should be permanently discontinued from the study intervention and the study.

If a participant has any other laboratory abnormality of Grade 3 or 4, confirmation needs to be obtained by a repeat test (centrally), to be performed within 48 hours of the result being available at the site. If confirmed, the participant should be permanently discontinued from the study intervention (see Section 7.1).

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's parent(s)/caregiver(s) (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For complications related to RSV disease as listed in Section 8.1.1.2 (see also Section 10.18, Appendix 18 for definitions and diagnostic criteria), additional data related to these events are collected when available and will be captured separately in the eCRF. Management of these events will be at the discretion of the investigator and should follow generally accepted medical standards.

Anticipated events for this study are defined in Section 8.3.4 and will be recorded and reported as described in Section 8.3.4, Regulatory Reporting Requirements for Serious Adverse Events.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 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 main ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

For participants with only a signed pre-screening (diagnostic) ICF (ie, for whom consent was not given to enroll in the main study by the parent[s]/caregiver[s] 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. 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 eCRF, 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 event should be transmitted electronically.

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's parent(s)/caregiver(s) 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.

AEs will be followed by the investigator as specified in Section 10.4, Appendix 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 following SAEs will be considered anticipated events:

- Cyanosis
- Pneumonia
- Bronchiolitis
- Respiratory failure
- Rhinitis
- Apnea
- Co-infections (bacterial or viral)

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 treatment 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. Adverse Events / Safety Topics of Special Interest

The following only applies to AEs starting after initiation of study intervention.

8.3.5.1. Hepatobiliary Effects

Given the hepatobiliary-related nonclinical findings and because the amount of clinical data is limited, the sponsor considers hepatobiliary effects to be a safety topic of special interest.

Hepatobiliary function will be evaluated by routine hepatobiliary function tests during the study.

In addition, a liver safety management plan is implemented based on ALT elevation. This liver safety management plan applies to screening results after the laboratory results become available to the site (refer to Section 10.8, Appendix 8).

Grading of ALT elevation will be based on the Division for Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Table (see Section 10.5, Appendix 5).

In case ≥ Grade 2 alkaline phosphatase (ALP) increase, additional laboratory assessments (such as γ-glutamyltransferase [GGT] and/or 5'-nucleotidase [5'NT]) may be performed as reflex testing for further evaluation of origins of elevation of potential hepatobiliary enzymes (see Section 10.2, Appendix 2 and Section 10.6, Appendix 6).

For any Grade 3 or 4 laboratory abnormalities that occurred at Day 8, Day 21 and Day 35 visits, participants should have a confirmatory measurement, 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 ALT elevation. During the study, these assessments will be captured as unscheduled assessments/visits.

8.3.5.2. 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.

A participant's study intervention must be discontinued if the participant has a confirmed QTcF value ≥500 msec at any scheduled visit based on the machine read QTcF value. Confirmation needs to be obtained during the same visit day by repeat ECG recording locally at the site (see Section 7.1). For participants with a confirmed QTcF interval value ≥500 msec during the treatment period, 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.
- 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

central laboratory. In case of hypokalemia and/or hypomagnesemia at screening or Day 8, the levels of potassium and/or magnesium should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at local laboratory) may be required.

- Appropriate clinical monitoring per local SOC, including ECG, should be installed. An ECG should be repeated every 24 hours until resolution of QTcF interval prolongation is confirmed. The participants 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

A blood sample for determination of rilematovir concentrations will be collected through finger prick or heel stick at 2 timepoints (see Section 1.3.3, Pharmacokinetic Assessments Sampling Schedule).

The following times need to be recorded: date and time of last study intervention intake, date and time of PK blood sampling, and time of any meal consumed within 30 minutes before or after the previous study intervention intake.

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

Residual samples after PK analysis can also be used for the analysis of metabolites of rilematovir, protein binding, or endogenous markers for enzymes or transporters involved in the metabolism and distribution of rilematovir or RSV-related biomarkers, at the discretion of the sponsor.

Residual blood samples collected for PK may also 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

Samples will be used for determination of rilematovir concentrations. Samples can also be used for the analysis of metabolites of rilematovir, protein binding, or endogenous markers for enzymes or transporters involved in the metabolism and distribution of rilematovir or RSV-related biomarkers, at the discretion of the sponsor.

8.4.2. Analytical Procedures

Pharmacokinetics

Samples will be analyzed (applicable treatment group only [not the placebo group]) to determine concentrations of rilematovir and/or metabolites as applicable using a validated, specific, and sensitive method by or under the supervision of the sponsor.

8.4.3. Pharmacokinetic Parameters and Evaluations

Population PK analysis 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 (ie, Phase 1 and Phase 2 studies) to support a relevant structural model. Available baseline participant characteristics (eg, demographics, body weight, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. The results of the population PK 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.

8.5. Pharmacokinetic/Pharmacodynamic Evaluations

Obtained PK and PD data (selected antiviral activity parameters, clinical outcomes, and safety parameters) will be used to explore the relationship between the PK and PD.

8.6. Medical Encounters

Medical encounters will be collected in the eCRF for all participants from time for presentation at the hospital/clinic throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

Number and duration of medical care encounters and treatments (including physician or emergency room visits, tests and procedures, and medications, surgeries and other selected procedures; inpatient and outpatient).

8.7. Acceptability and Palatability

Acceptability and palatability of the rilematovir formulation will be assessed through a questionnaire completed by parent(s)/caregiver(s) on an electronic device after last dosing (see Section 10.16, Appendix 16).

8.8. Biomarkers

No specific samples will be collected for biomarker research. Leftover blood samples and leftover nasal MT swab samples from samples collected during the study may be used for exploratory biomarker analyses (eg, proteins, RNA, immune cells, microbiome) at the sponsor's discretion and results may be reported separately from this study.

8.9. Detection of Baseline Presence of Other Respiratory Viruses and Bacteria

The presence of other respiratory viruses (other than RSV) or bacteria will be assessed in the nasal MT swab sample collected at baseline by PCR assay at the central laboratory. Central testing for other respiratory viruses will also include testing for the presence of SARS-CoV-2 in the nasal MT swab sample. Nasal MT swabs from other time points may also be assessed for detection of other respiratory viruses or bacteria at the central laboratory, if deemed necessary.

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 and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

The primary analysis will be performed when all randomized participants have completed the final study visit or discontinued earlier.

9.1. Statistical Hypotheses

The primary hypothesis is that treatment with rilematovir improves clinical outcome of RSV infection as compared to placebo in hospitalized pediatrics as assessed on the RRS on the first study day when at least 50% of the participants across treatment arms are discharged from the hospital.

9.2. Sample Size Determination

The study will aim to enroll 737 participants. Participants will be randomized 2:1 (active:placebo) to receive either rilematovir or placebo.

The sample size calculation is based on the primary endpoint, ie, the RRS and results from Study 53718678RSV2002. The study day on which the RRS will be assessed as the primary endpoint is the first study day when at least 50% of the participants across treatment arms are discharged from the hospital (with or without signs/symptoms). This study day will be determined in a blinded manner based on all available data irrespective of the treatment group at the time of the first interim analysis and by an independent statistician in order to protect data integrity. This study day will be used for any further interim analysis as well as for the final analysis.

Based on the proportional odds model and assuming a benefit of approximately 45% reduction of the common odds ratio, a total sample size of 700 participants (randomized 2:1) would provide a power of at least 95%, using an overall Type 1 error rate of 5% (2-sided) and accounting for the group-sequential design.[42] A reduction of 35%, which is still considered clinically relevant, would provide a power of 80%. Assuming 5% of participants will be excluded from the primary analysis set (intent to treat - infected [ITT-i] set), the total sample size for this study is 737.

In the sample size calculation, it is assumed that the distribution of participants treated with placebo between the categories of the RRS will be as follows on the selected study day:

- Not hospitalized without signs/symptoms: 20%
- Not hospitalized with signs/symptoms: 20%
- Non-ICU hospitalization, not requiring supplemental oxygen nor supplemental feeding/hydration: 15%
- Non-ICU hospitalization, requiring supplemental oxygen and/or supplemental feeding/hydration: 30%
- Admitted to the ICU, not requiring mechanical ventilation: 7%
- Requiring mechanical ventilation: 7%
- Death: 1%

The sample size is robust to mild to moderate changes to this distribution.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed 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 an RSV infection confirmed by central laboratory analysis. Participants with confirmed SARS-CoV-2 infection (positive test by central laboratory analysis) are excluded. This population will be used for the analysis of efficacy endpoints, as randomized.
Safety	All participants who took at least 1 dose of study intervention. This population 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 population PK analysis 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

Further details will be provided in the SAP.

Participant Information

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

All demographic (eg, age, length, weight, race, gender) and other initial participant characteristics (physical examination [length, body weight, head circumference], medical and surgical history, family history, concomitant diseases, RSV disease characteristics) will be tabulated and analyzed descriptively by treatment group.

9.4.2. Efficacy Analyses

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, a hierarchical testing procedure will be applied to control for the overall Type I error rate at the 5% level (2-sided). The following endpoints are included in the confirmatory testing strategy:

1. RRS, ie, the primary endpoint.
2. Proportion of participants clinically resolved from RSV disease (based on ClinRO Signs/Symptoms as assessed at the same study day as the primary endpoint).
3. Time from first dosing to resolution of Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms and supplementation-free for at least 24 hours.
4. Time from discharge to resolution of Key RSV Signs/Symptoms based on ObsRO Signs/Symptoms (for participants who did not reach resolution before first discharge).
5. Time from first dosing to end of oxygen supplementation (for participants who were receiving supplemental oxygen at the time of first dosing).
6. Incidence in post-baseline RSV-related complications.

First, the primary endpoint will be tested for superiority of rilematovir over placebo at the 2-sided 5% significance level. If superiority is shown on the primary endpoint, then the first secondary endpoint indicated by "2." in the sequence above will be tested for superiority at the 2-sided 5% significance level. If superiority is shown for this secondary endpoint, further secondary endpoints will be tested for superiority in the sequence as indicated above, and at the same significance level. In case superiority is not shown for an endpoint, no further endpoints in the sequence will be tested for superiority.

9.4.2.1. Primary Endpoint

The study day on which the RRS will be assessed as the primary endpoint is the first study day when at least 50% of the participants across treatment arms are discharged from the hospital (with or without signs/symptoms). This study day will be determined in a blinded manner based on all available data irrespective of the treatment group at the time of the first interim analysis and by an independent statistician in order to protect data integrity. This study day will be used for any further interim analysis as well as for the final analysis.

A proportional odds model will be used to analyze the RRS, including treatment, RRS category at baseline, and the two stratification factors (stratification by presence of [a] risk factor[s] for severe RSV disease versus otherwise healthy and by region).

In addition, each of 6 dichotomizations of the RRS, ie:

- Not hospitalized without signs/symptoms, vs worse
- Not hospitalized with signs/symptoms (or better), vs worse
- Non-ICU hospitalized not requiring supplemental oxygen nor supplemental feeding/hydration (or better), vs worse
- Non-ICU hospitalized requiring supplemental oxygen and/or feeding/hydration (or better), vs worse
- Admitted to the ICU not requiring mechanical ventilation (or better), vs worse
- Requiring mechanical ventilation (or better), vs worse (ie, died)

will be analyzed using a logistic regression model, including treatment, RRS category at baseline, and stratification factors.

9.4.2.1.1. Estimand

The primary estimand attributes are as follows:

A. Study intervention:

- Rilematovir + standard-of-care (SOC)
- Placebo + SOC

B. Population:

Hospitalized children ≤5 years of age, diagnosed with moderate to severe, central laboratory confirmed RSV infection, randomized within onset of first RSV signs/symptoms ≤3 days and without SARS-CoV-2 infection as confirmed by central laboratory analysis.

C. Variable:

RRS at Study Day X based on protocol-defined categories, ie, the categories to which the participant should be assigned based on the data reported in the eCRF and eCOA, rather than the category where (s)he may actually be. The Study Day X is the first study day when at least 50% of the participants across intervention groups are discharged from the hospital and will be determined in a blinded manner at the time of the first interim analysis.

D. Summary measure (Population-level summary):

The common odds ratio will be estimated by a proportional odds model.

E. Intercurrent events:

Intercurrent Event (ICE)	Strategy Addressing ICEs and Its Description
Discontinuation of study intervention prior to Day 7/8*	**Treatment policy**: all data will be used regardless of occurrence of the intercurrent event
Selected major protocol deviations due to: • Use of prohibited medication • Missing 2 or more doses	**Treatment policy**: all data will be used regardless of the occurrence of major protocol deviations
Use of any symptomatic medication (ie, initiation or change in regimen)	**Treatment policy**: all data will be used regardless of occurrence of the intercurrent event
COVID-19 vaccination	**Treatment policy:** all data will be used regardless of occurrence of the intercurrent event
Death	**Composite**: it is one of the categories of the RRS

*Day 7 evening if first study intervention administration took place in the morning. Day 8 morning if initial administration of study intervention took place in the evening.

Missing data will be handled as follows:

- Participants with RRS category missing before discharge will be imputed as follows:

  For participants without ICE occurring prior to the study day of RRS evaluation, missing RRS category will be assumed Missing-at-Random (MAR) and will be multiply imputed based on information from within their own study intervention group.

  For participants with ICE occurring prior to the study day of RRS evaluation, missing RRS category will be assumed Missing-Not-at-Random (MNAR) and will be multiply imputed based on information from the placebo group.

- Missing ObsRO after the participant discharged from the hospital (RRS Category 1 or 2), a 2-step approach will be considered:

  a. If ObsRO is missing in between 2 days on which ObsRO is available, then it will be imputed as indicated in the table below.

Previous Study Day Available	Next Study Day Available	Imputed Value	RRS Category
Resolved	Resolved	Resolved	Not Hospitalized Without Signs/Symptoms
Not resolved	Not resolved	Not resolved	Not Hospitalized With Signs/Symptoms
Resolved	Not resolved	Not resolved	Not Hospitalized With Signs/Symptoms
Not resolved	Resolved	Not resolved	Not Hospitalized With Signs/Symptoms

RRS = RSV Recovery Scale

  b. In any other situation, the worst-case scenario of the 2 home categories will be selected, ie, “Not Hospitalized With Signs/Symptoms”.

9.4.2.2. Key Secondary Endpoint(s)

For the hypothesis testing, the following methods will be used:

- Time from first dosing to resolution of Key RSV Signs/Symptoms (based on ObsRO Signs/Symptoms), time from discharge to resolution of Key RSV Signs/Symptoms (based on ObsRO Signs/Symptoms) and time from first dosing to end of oxygen supplementation will be analyzed using a stratified Gehan-Wilcoxon test (using the randomization stratification factors).
- To compare the proportion of participants clinically resolved from RSV (based on ClinRO Signs/Symptoms), a logistic regression model will be used. Randomization stratification factors will be added to the model. A similar model will be applied to analyze the incidence of treatment-emergent RSV-related complications.

9.4.2.3. Clinical Course of RSV Infection

Endpoints related to evaluation of the clinical course of RSV infection will be analyzed graphically and descriptively as described in the statistical analysis plan SAP. For continuous variables, descriptive statistics (including: n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented. Time to-variables will be analyzed using KM plots and will be modeled using an accelerated failure time model, adjusted for the randomization stratification factors, to estimate differences between intervention groups.

More details regarding the analysis, including subgroup analyses, of these data will be described in the SAP.

9.4.2.4. Antiviral Activity

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

Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood-based repeated measures approach. 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 95% 2-sided confidence intervals.

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

9.4.2.5. 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.

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population.

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 or any worsening of an pre-existing condition occurring at or after the initial administration of study intervention through the end of the study is considered to be treatment-emergent AE (TEAE). All reported TEAEs will be included in the analysis. For each TEAE, 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 AE or an SAE, or who experience anticipated events.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results 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 or with any markedly abnormal laboratory results will be provided.

The laboratory abnormalities will be graded per the criteria specified in the DMID (see Section 10.5, Appendix 5) pediatric toxicity tables and in accordance with the normal ranges of the clinical laboratory if no DMID gradings were available. ALP will be graded per the criteria specified in the Division of Acquired Immunodeficiency Syndrome (DAIDS) adult and pediatric toxicity table (see Section 10.6, Appendix 6). For breast feeding neonates, total bilirubin will also be graded per the DAIDS adult and pediatric toxicity tables (see Section 10.6, Appendix 6).

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 QTc interval using the following correction methods: QTcB and QTcF.[25]

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 msec, >480 msec, or

>500 msec will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 and ≤60 msec or >60 msec.

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).

Vital Signs

Descriptive statistics of actual values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.4. Other Analyses

9.4.4.1. Pharmacokinetic Analyses

Population PK analysis of 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 population PK analysis plan and the results of the population PK analysis 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 population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available whole blood 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 including exposure information of rilematovir, and, if applicable, of metabolites and/or endogenous markers.

9.4.4.2. 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.

PK/PD analyses may be conducted at the sponsor's discretion and reported in a separate report.

9.4.4.3. Biomarkers Analyses

Statistical approaches to explore correlations between clinical outcome, viral load, and biomarkers in blood (and potentially in nasal MT swab samples) 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.

9.4.4.4. Medical Encounters

Medical encounters will be descriptively summarized by intervention group.

9.4.4.5. Acceptability and Palatability

Data on acceptability and palatability of the rilematovir formulation will be presented descriptively.

9.5. Interim Analyses

Two interim analyses are planned. Each interim analysis will preferably be conducted at the end of a Northern or Southern hemisphere RSV season. The first interim analysis will be performed at the end of the first season where the cumulative enrollment reaches approximately 35% of the total sample size and will include an assessment of futility. The second interim analysis will be performed at the end of the first season where the cumulative enrollment reaches approximately 75% of the total sample size and will include an assessment of futility and stopping for early superiority. An additional interim analysis with assessment of stopping for early superiority might be performed at the end of an RSV season after the second pre-planned interim analysis, provided that approximately 85% of the total sample size is enrolled.

To account for the evaluation of early superiority at the second and at the optional additional interim analyses, a group-sequential approach using the O'Brien Fleming type alpha spending function will be used to calculate the significance level for each analysis, based on the total sample size and the actual number of participants included in the interim analysis.

The interim analyses will be implemented through an IDMC providing recommendations to a Sponsor Committee. Only the IDMC and the independent Statistical Support Group will be unblinded to the data.

Details on the planned interim analyses and the statistical decision rules will be provided in the IDMC Charter and SAP.

9.6. Independent Data Monitoring Committee

An IDMC will be established as noted in Committees Structure in Section 10.3.6 in Appendix 3.

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 IDMC will perform the first unblinded safety review when approximately 10% of the participants have

completed the Day 14 assessments (or discontinued earlier). The committee will meet periodically to review safety data and results from the interim analyses. After each review, the IDMC will provide recommendations regarding the continuation of the study to the Sponsor Committee.

After the first interim analysis, the IDMC will also provide a recommendation regarding the initiation of the neonatal substudy.

Once the last participant of the last cohort of the substudy in neonates has completed Day 14 assessments (or discontinued earlier), the IDMC will review the data and recommend whether enrollment of neonates into this main study can be opened and which dosing regimen is to be used for neonates. Investigators and relevant health authorities, ethics committees, and IRBs will be informed in writing of the decision and the selected dosing regimen for neonates.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

5'NT	5'-nucleotidase
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
ARI	acute respiratory infection
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve / area under the RSV viral load-time curve
AUC_{0-xh}	AUC from time of administration up to time x,
$AUC_{0-\infty}$	AUC from time of administration extrapolated to infinity
BCRP	breast cancer resistance protein
bid	twice daily
BUN	blood urea nitrogen
CI	confidence interval
ClinRO	Clinician Reported Outcome
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNEP	continuous negative extra-thoracic pressure
CNP	continuous negative pressure
CNS	central nervous system
COA	clinical outcome assessment
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CTC	Common Toxicity Criteria
C_{trough}	predose plasma concentration
C_{xh}	plasma concentration x hours after time of administration
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBP	diastolic blood pressure
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
EAE	emergent AE
EC_{50}	effective concentration for 50% inhibition
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
eDC	electronic data capture
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GGT	γ-glutamyltransferase
GHQ	General Health Questions
hERG	human-ether-a-gogo-related
HIV	human immunodeficiency virus
HP-β-CD	2-Hydroxypropyl-beta-cyclodextrin
IB	Investigator's Brochure
ICE	Intercurrent Event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT-i	intent to treat – infected
IV	intravenous/intravenously
IWRS	interactive web response system
KM	Kaplan-Meier
LLN	lower limit of normal
LRTC	lower respiratory tract complications
LRTI	lower respiratory tract infection
MAR	Missing-at-Random
MCH	mean cell hemoglobin
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing-Not-at-Random
MRU	medical resource utilization
MT	mid-turbinate
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
OATP	organic-anion-transporting polypeptide
OCT	organic cation transporter
ObsRO	Observer Reported Outcome
PBPK	physiologically based PK
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PEEP	positive end-expiratory pressure
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
PQC	Product Quality Complaint
PRESORS	Pediatric RSV Electronic Severity and Outcome Rating Systems
PT	prothrombin time
q24h	every 24 hours
qd	once daily
qRT-PCR	quantitative reverse transcription polymerase chain reaction
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTcI	individual-corrected QT
RBC	red blood cell
RNA	ribonucleic acid
RRS	RSV Recovery Scale
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SOA	Schedule of Activities
SOC	standard-of-care
SpO_2	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2term}$	terminal elimination half-life
TDRM	total drug related material
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum plasma concentration
TQT	thorough QT
TR	total radioactivity

UGT	glucuronyl transferase
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
WBC	white blood cell
WHO	World Health Organization

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell (RBC) count
Hemoglobin
Hematocrit
% Reticulocytes</td><td><u>RBC Indices:</u>
MCV
MCH
MCH concentration</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">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.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Blood urea nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
γ-glutamyltransferase (GGT)*
5'-nucleotidase (5'NT)*</td><td>Total bilirubin (direct and indirect)
Alkaline phosphatase
Uric acid
Magnesium
Sodium
Potassium
Chloride
Bicarbonate
Calcium</td></tr>
<tr><td colspan="3">Note: Levels of potassium and magnesium to be determined by the central laboratory. In case of hypokalemia and/or hypomagnesemia at screening or Day 8, the levels of potassium and/or magnesium should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances.

*As reflex testing in case ≥ Grade 2 alkaline phosphatase (ALP) increase (Section 10.6, Appendix 6)</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment (if dipstick result is abnormal)</u>
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="3">If dipstick result (local test) is abnormal, microscopy will be used to measure sediment. Microscopy will be done in the central laboratory and results do not need to be captured in the eCRF.</td></tr>
</table>

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 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.

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.

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 one 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's parent(s)/legally acceptable representative(s) 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's parent(s)/legally acceptable representative(s) 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.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participant's parent(s)/legally acceptable representative(s) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants' parent(s)/legally acceptable representative(s) will be informed that the infant's/child's/neonate's participation in the study 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. 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's parent(s)/legally acceptable representative(s) is/are authorizing such access.

Prior to signing the main ICF for the study, participant's parent(s)/legally acceptable representative(s) may specifically allow for the collection and testing of nasal MT swab by signing the pre-screening (diagnostic) ICF. This is not required if a positive RSV diagnostic result based on a study-specific local SOC sample collected within 48 hours prior to anticipated randomization is available and used for determining study eligibility.

The participant's parent(s)/legally acceptable representative(s) 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 parent(s)/legally acceptable representative(s) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant's parent(s)/legally acceptable representative(s).

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

If the participant's parent(s)/legally acceptable representative(s) is/are unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant's parent(s)/legally acceptable representative(s) is obtained.

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's parent(s) (or his or her legally acceptable representative) 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's parent(s) (or his or her legally acceptable representative) has/have the right to request through the investigator access to the participant's 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 biomarker 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 left-over after study-specific testing may be stored for up to 15 years (or according to local regulations) for scientific and biomarker research if the participant's parent(s)/legally acceptable representative(s) consent. Samples will only be used to understand RSV disease, to understand rilematovir, to understand differential drug 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 IDMC will perform the first unblinded safety review when approximately 10% of the participants have completed the Day 14 assessments (or discontinued earlier). The committee will meet periodically to review safety data and results from the interim analysis. After each review, the IDMC will provide recommendations regarding the continuation of the study to the Sponsor Committee. At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or to the safety assessments to the Sponsor Committee to ensure the safety of enrolled participants.

The IDMC will consist of at least 3 members, including one medical expert in respiratory infectious diseases, one cardiovascular expert knowledgeable about pediatric 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.

After the first interim analysis, the IDMC will provide a recommendation regarding the initiation of the neonatal substudy.

Once the last participant of the last cohort of the substudy in neonates has completed Day 14 assessments (or discontinued earlier), the IDMC will review the data and recommend whether enrollment of neonates into this main study can be opened and which dosing regimen is to be used for neonates.

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.

Investigators and relevant health authorities, ethics committees, and institutional review boards (IRBs) will be informed in writing of the decision and the selected dosing regimen for neonates.

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, and direct transmission of clinical laboratory data from a central laboratory (if applicable) into the sponsor's database and direct transmission of clinician PRESORS and parent(s)/caregiver(s) PRESORS, Caregiver Impact Questions, and Acceptability and Palatability Assessment data to the electronic device vendor database and then to the sponsor’s database. 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 the 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 the 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 eCRF 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 eDC tool. If corrections to a 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.

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 other equivalent document).

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the

eCRF in the protocol include the electronic source system but information collected through electronic source may not be limited to that found in the eCRF. Data in this system may be considered source documentation. The following data will be recorded directly on the electronic device and will be considered source data: clinician PRESORS and parent(s)/caregiver(s) PRESORS, Caregiver Impact Questions, and Acceptability and Palatability Assessment.

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 data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF 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 (s)he 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 eCRF 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 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 medicinal (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 International Conference on Harmonisation [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 main ICF (refer to All Adverse Events under Section 8.3.1 for time of last AE recording). For participants with only a signed pre-screening (diagnostic) ICF (ie, for whom consent was not given to enroll in the main study by the parent[s]/caregiver[s] by signing the main ICF), only study procedure related AEs will be reported.

Serious Adverse Event

An SAE based on ICH and EU 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.

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.

10.4.2. Attribution Definitions

Assessment of Causality

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

Related

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

Not Related

There is not a reasonable causal relationship between study treatment 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, as per DMID (see Section 10.5, Appendix 5) or per DAIDS for bilirubin for breast feeding neonates and for ALP (see Section 10.6, Appendix 6), will be made.

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)

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

AEs will be reported by the participant's parent(s)/legally acceptable representative(s) (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study (see Section 8.3.1).

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 eCRF. 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 eCRF 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's parent(s)/legally acceptable representative(s) must be provided with a "wallet (study) card" and instructed to keep this card with the participant 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 perform 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 discontinuation of the participant's participation in 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 rehospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE.

The cause of death of a participant in the study within 30 days after the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE and must be reported using the Serious Adverse Event Form.

Anticipated events:

- Cyanosis
- Pneumonia
- Bronchiolitis
- Respiratory failure
- Rhinitis
- Apnea
- Co-infections (bacterial or viral)

10.4.6. Product Quality Complaint Handling

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: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007, draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
Rx = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	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 or death*: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

* The draft DMID pediatric toxicity tables characterize death as a Grade 5 event, for the purposes of this study the sponsor will categorize events into 4 grades and has included death with life-threatening in the Grade 4 category.

SERIOUS OR LIFE-THREATENING ADVERSE EVENTS

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, National Cancer Institute's [NCI's] Common Toxicity Criteria [CTC], and 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.

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Selected Values for children less than or equal to 3 months of age – does not apply to preterm infants)

For all parameters not listed in this table, please refer to the DMID Toxicity Table for children >3 months of age

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin				
1-7 days old	13.0-14.0 g/dL	12.0-12.9 g/dL	<12 g/dL	Cardiac Failure secondary to Anemia
8-21 days old	12.0-13.0 g/dL	10.0-11.9 g/dL	<10.0 g/dL	Cardiac Failure secondary to Anemia
22-35 days old	9.5-10.5 g/dL	8.0-9.4 g/dL	<8.0 g/dL	Cardiac Failure secondary to Anemia
36-60 days old	8.5-9.4 g/dL	7.0-8.4 g/dL	<7.0 g/dL	Cardiac Failure secondary to Anemia
61-90 days old	9.0-9.9 g/dL	7.0-8.9 g/dL	<7.0 g/dL	Cardiac Failure secondary to Anemia
Absolute Neutrophil Count				
1 day old	5000-7000/mm^3	3000-4999/mm^3	1500-2999/mm^3	<1500/mm^3
2-6 days old	1750-2500/mm^3	1250-1749/mm^3	750-1249/mm^3	<750/mm^3
7-60 days old	1200-1800/mm^3	900-1199/mm^3	500-899/mm^3	<500/mm^3
61-90 days old	750-1200/mm^3	400-749/mm^3	250-399/mm^3	<250/mm^3

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Selected values for children younger than or aged 3 months)

HEMATOLOGY (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (fractionated bilirubin test must be performed when total bilirubin is elevated)				
<7 days old	-	20-25mg/dL	26-30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN
Creatinine				
<7 days old	1.0-1.7 mg/dL	1.8-2.4 mg/dL	2.5-3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5-0.9 mg/dL	1.0-1.4 mg/dL	1.5-2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6-0.8 mg/dL	0.9-1.1 mg/dL	1.2-1.5 mg/dL	>1.5 mg/dL
Creatinine Clearance				
<7 days old	35-40 mL/min	30-34 mL/min	25-29 mL/min	<25 mL/min
7-60 days old	45-50 mL/min	40-44 mL/min	35-39 mL/min	<35 mL/min
61-90 days old	60-75 mL/min	50-59 mL/min	35-49 mL/min	<35 mL/min
Hypocalcemia				
<7 days old	6.5-6.9 mEq/L	6.0-6.4 mEq/L	5.5-5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6-8.0 mEq/L	7.0-7.5 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8-8.4 mEq/L	7.0-7.7 mEq/L	6.0-6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0-12.4 mEq/L	12.5-12.9 mEq/L	13.0-13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5-11.2 mEq/L	11.3-11.9 mEq/L	12.0-13.0 mEq/L	>13.0 mEq/L

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

LOCAL REACTIONS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Induration	<10 mm	10-25 mm	26-50 mm	>50 mm
Erythema	<10 mm	10-25 mm	26-50 mm	>50 mm
Edema	<10 mm	10-25 mm	26-50 mm	>50 mm
Rash at Injection Site	<10 mm	10-25 mm	26-50 mm	>50 mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin for children older than 3 months and younger than 2 years of age	9.0 - 9.9 g/dL	7.0 - 8.9 g/dL	<7.0 g/dL	Cardiac Failure secondary to anemia
Hemoglobin for children older than 2 years of age	10 - 10.9 g/dL	7.0 - 9.9 g/dL	<7.0 g/dL	Cardiac Failure secondary to anemia
Absolute Neutrophil Count	750 - 1200/mm^3	400 - 749/mm^3	250 - 399/mm^3	<250/mm^3
Platelets	-------	50,000 - 75,000/mm^3	25,000 - 49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1 - 1.2 x ULN	1.3 - 1.5 x ULN	1.6 - 3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1 - 1.6 x ULN	1.7 - 2.3 x ULN	2.4 - 3.0 x ULN	>3.0 x ULN

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (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
Bilirubin (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
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
Pancreatic Amylase	1.1 - 1.4 x ULN	1.5 - 1.9 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
Uric Acid	7.5 - 9.9 mg/dL	10 - 12.4 mg/dL	12.5 - 15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	-	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

GASTROINTESTINAL (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Constipation	Slight change in the consistency/frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and Vomiting
Nausea	Mild	Moderate-Decreased oral intake	Severe-Little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes per day	4-6 episodes per day	Greater than 6 episodes per day or Intractable Vomiting

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

ELECTROLYTES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
CREATININE **Note:** ULN are the adult ULN				
3 months - 2 years of age	0.6 - 0.8 x ULN	0.9 - 1.1 x ULN	1.2 - 1.5 x ULN	>1.5 x ULN
2 years - 12 years of age	0.7 - 1.0 x ULN	1.1 - 1.6 x ULN	1.7 - 2.0 x ULN	>2.0 x ULN
Older than 12 years of age	1.0 - 1.7 x ULN	1.8 - 2.4 x ULN	2.5 - 3.5 x ULN	>3.5 x ULN
Hypernatremia	-	>145 - 149 mEq/L*	150 - 155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia	-	130 - 135 mEq/L	129 - 124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0 - 5.9 mEq/L	6.0 - 6.4 mEq/L	6.5 - 7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0-3-5 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5 - 11.2mg/dL	11.3 - 11.9 mg/dL	12.0 - 12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.0 - 6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2 - 1.4 mEq/L	0.9 - 1.1 mEq/L	0.6 - 0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55 - 65 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116 - 159 mg/dL	160 - 249 mg/dL	250 - 400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic ≥25 cells/hpf*	----	Gross hematuria

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

CENTRAL NERVOUS SYSTEM (CNS)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Generalized CNS Symptoms	-	-	Dizziness	Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia ; Inconsolable crying >3 hrs;
Headache	Mild	Moderate, Responds to non-narcotic analgesia	Moderate to Severe, Responds to narcotic analgesia	Intractable
Level of Activity	-	Slightly irritable OR slightly subdued	Very irritable OR Lethargic	Inconsolable OR Obtunded
Visual	-	Blurriness, diplopia, or horizontal nystagmus of <1 hour duration, with spontaneous resolution	More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis
Myelopathy	-	None	None	Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuropathy/ Lower Motor Neuropathy	-	Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

(Older than 3 months of age)

OTHER				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	-	38.5 - 40.0°C 101.3 – 104.0 °F	Greater than 40.0°C Greater than 104.0°F	Sustained Fever: Equal or greater than 40.0°C (104.0°F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study intervention	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study intervention	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study intervention must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study intervention

*Revised by the sponsor

10.6. Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1; July 2017)

Alkaline phosphatase for pediatrics and total bilirubin for term and preterm neonates.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Total Bilirubin,[a] High (mg/dL; *µmol/L*)[b]				
Term Neonate[c] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[b] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[a] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[b] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[c] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

10.7. Appendix 7: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	0 - 2 yrs	NA	>150
	>2 - 5 yrs	NA	>160
QRS (msec)	0 - 2yrs	NA	>89
	>2 - 5 yrs	NA	>95
QTc (msec)	0 - 5 yrs	NA	>500
RR (msec)	0 - 3 mo	<333	>750
	3 - 12 mo	<400	>860
	1 - 2 yrs	<430	>1,000
	2 - 18 yrs	<600	>1,200

Vital Signs

The following clinically relevant abnormalities will be defined for vital signs

Parameter (unit)		Age class				
		0 – 3 mo	3 – 12 mo	1 – <2 yrs	2 – <3 yrs	3 – ≤5yrs
Diastolic BP (mmHg)	abnormally low	<35	<40	<40	<40	<45
	abnormally high	>65	>85	>90	>70	>85
Systolic BP (mmHg)	abnormally low	<60	<60	<75	<80	<80
	abnormally high	>110	>110	>120	>110	>125
Heart rate HR (bpm)	abnormally low	<80	<70	<60	<90	<70
	abnormally high	>180	>150	>140	>130	>130
Respiration rate	abnormally low	<25	<20	<18	<20	<20
	abnormally high	>70	>60	>50	>35	>45
Oxygen saturation SpO_2 (%)	abnormally low	<92	<92	<92	<92	<92

References:

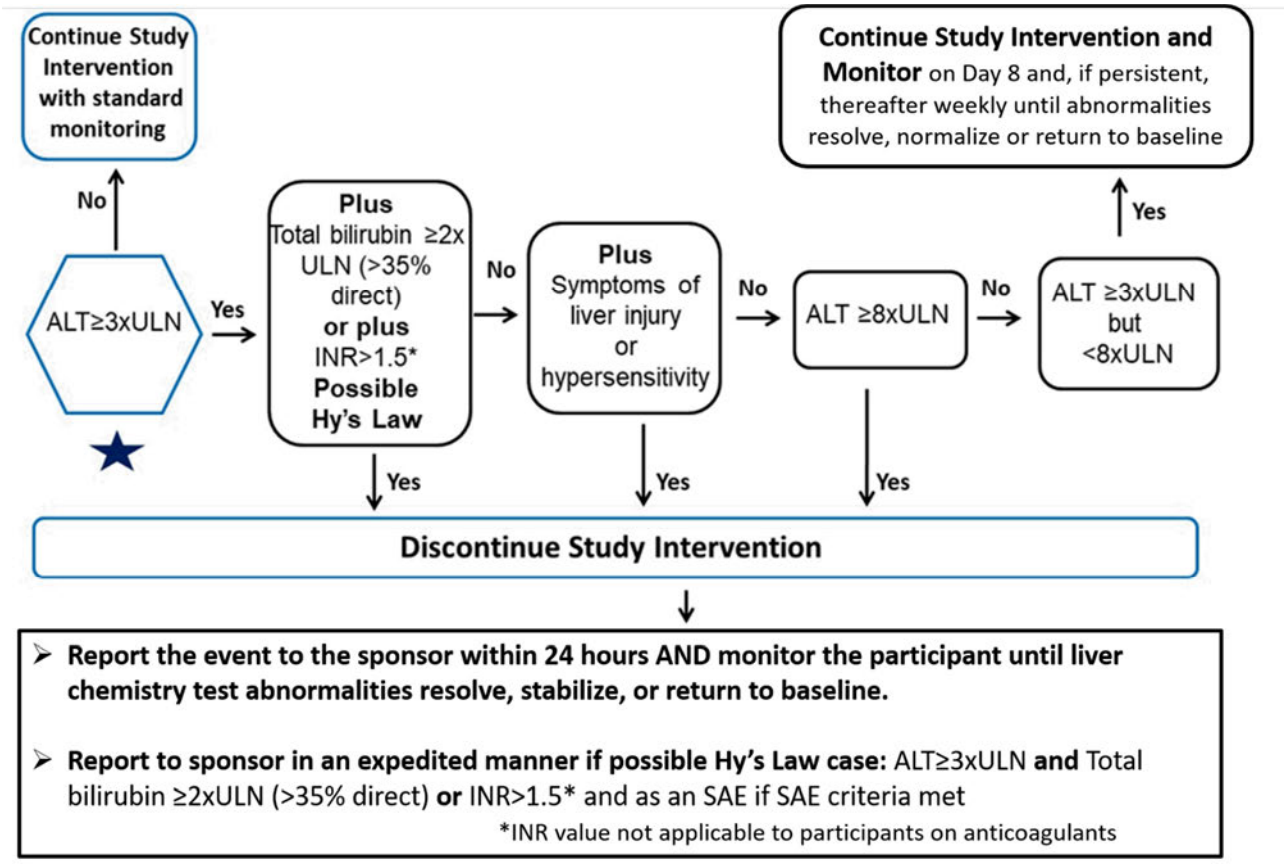
Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-1018.

10.8. Appendix 8: Liver Safety Plan: 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.

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.

10.9. Appendix 9: General Guidelines for Measuring Vital Signs and SpO_2

Variability in the measurement of vital signs and SpO_2 is to be expected due to a number of reasons; therefore, general guidelines for measuring vital signs and SpO_2 have been developed to have a more consistent approach across sites and countries related to the methodology for measuring these clinical parameters. In case the infant/child is crying or not calm or not supine (or lying on their parent's/caregiver's arm), resulting measurements should be recorded as not assessable in the eCRF.

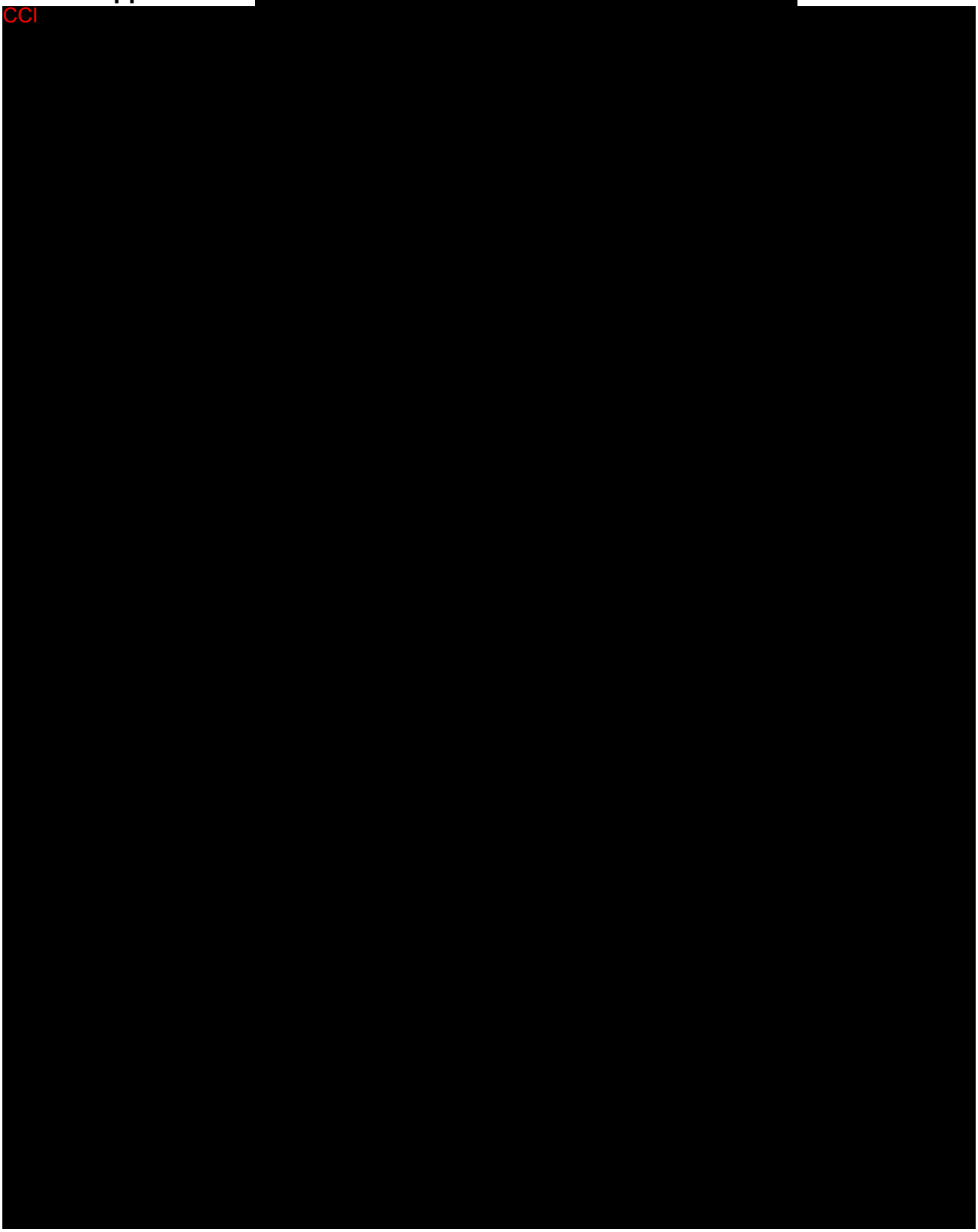
Parameter	General Instructions
Blood Pressure	• While the participant is hospitalized, if possible, use the same blood pressure measurement methodology for all patients enrolled at the site. • Prior to the measurement, the participant needs to be rested for at least 5 minutes and measurement is done preferably when the participant is sleeping or calm (ie, not crying or immediately after feeding). • The participant should be in supine position and the arm should be supported (eg, with a pillow). Infants can be lying on their parent's/caregiver's arm. • Blood pressure measurements should preferentially be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. • If an automated device is not available, a properly maintained mercury sphygmomanometer is preferred over aneroid and hybrid sphygmomanometers. When using a mercury sphygmomanometer, the mercury column should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mm Hg. • Preferentially, the standard location for blood pressure measurement is the upper arm, with the stethoscope at the elbow crease over the brachial artery (with manual technique). Clothing that covers the arm should be removed prior to the placement of the cuff. The cuff should be fitted for the size of the participant.
Heart/Pulse Rate	• While the participant is hospitalized, if possible, use the same heart/pulse rate measurement methodology for all patients enrolled at the site. • Prior to the measurement, the participant needs to be rested for at least 5 minutes and measurement is done preferably when the participant is sleeping or calm (ie, not crying or immediately after feeding). • The participant should be in supine position. Infants can be lying on their parent's/caregiver's arm. • Heart/pulse rate measurements should preferentially be assessed with a completely automated device. • Manual techniques will be used only if an automated device is not available. • If manual measurement, auscultation of the heart or pulse (radial, brachial) determination are considered acceptable. • If manual measurement, 30 seconds (minimum) or 1 minute (preferred) count are considered acceptable.

Respiratory Rate	• While the participant is hospitalized, if possible, use the same respiratory rate measurement methodology for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes and measurement is done preferably when the participant is sleeping or calm (ie, not crying or immediately after feeding). • The participant should be in supine position. Infants can be lying on their parent's/caregiver's arm. • Respiratory rate measurements can be assessed with an automated device or with manual measurement (no preference). • If manual measurement is used, inspection (preferred) or auscultation of the lungs (alternative) are considered acceptable. • If manual measurement, 30 seconds (minimum) or 1 minute (preferred) count are considered acceptable.
Temperature	• While the participant is hospitalized, if possible, use the same type of temperature measurement methodology for all participants enrolled at the site. • In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. • Electronic devices (tympanic, oral) are preferred over traditional mercury thermometers (for oral temperature). • Tympanic (preferred) or oral (alternative) temperature measurements are considered acceptable. Axillary temperature should be avoided since it provides the worst estimate of core temperature and it is largely influenced by environmental conditions.
SpO_2	• While the participant is hospitalized, if possible, use the same type of probe for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes and measurement is done preferably when the participant is sleeping or calm (ie, not crying or immediately after feeding). • The participant should be in supine position. Infants can be lying on their parent's/caregiver's arm. • Pulse oximetry measurements using finger, toe, earlobe or frontal sensors are considered acceptable. If using the digits, assess for warmth and capillary refill, since adequate arterial pulse strength is necessary for obtaining accurate SpO_2 measurements. • Avoid placing the sensor on sites distal to indwelling arterial catheters, blood pressure cuffs, or venous engorgement (eg, arteriovenous fistulas, blood transfusions). • For hospitalized participant receiving supplemental O_2, the supplemental O_2 should be interrupted until the SpO_2 drops below 92% and remains stable at that level for 1 minute, or up to 15 minutes, whichever comes first, before measuring SpO_2 for at least one of the scheduled assessments per day.

	• If it is determined by the investigator that it is unsafe to remove the participant's supplemental O_2 for assessment of O_2 saturation (eg, participant is on mechanical ventilation [invasive or non-invasive] or on high-flow mask), then SpO_2 should be measured while receiving supplemental O_2. It should be recorded in the eCRF that supplemental O_2 was not interrupted and the reason should be documented.

10.10. Appendix 10: CCI

CCI

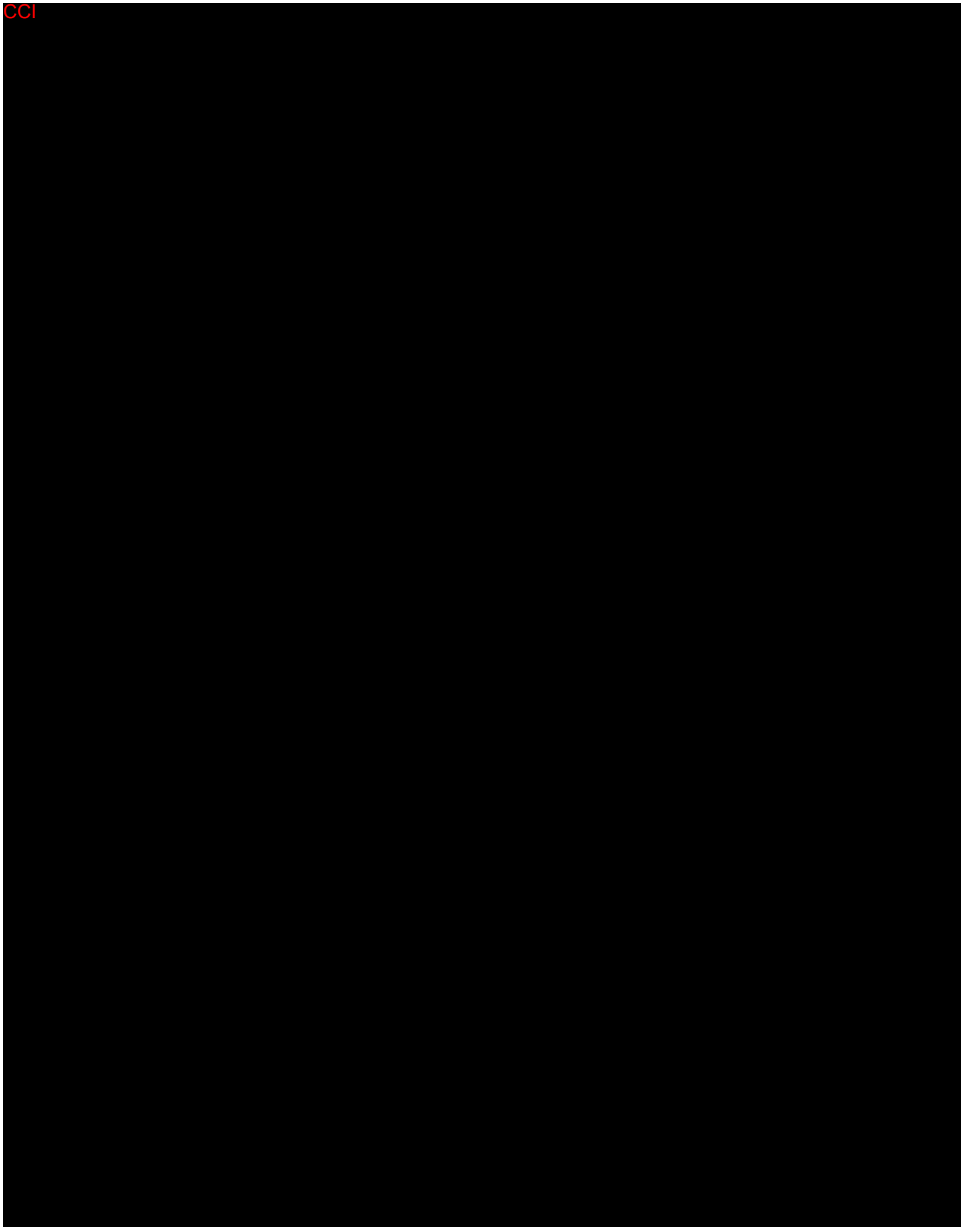


10.11. Appendix 11: CCI [redacted]

CCI [redacted]

CCI

[redacted]


CCI


CCI

CCI

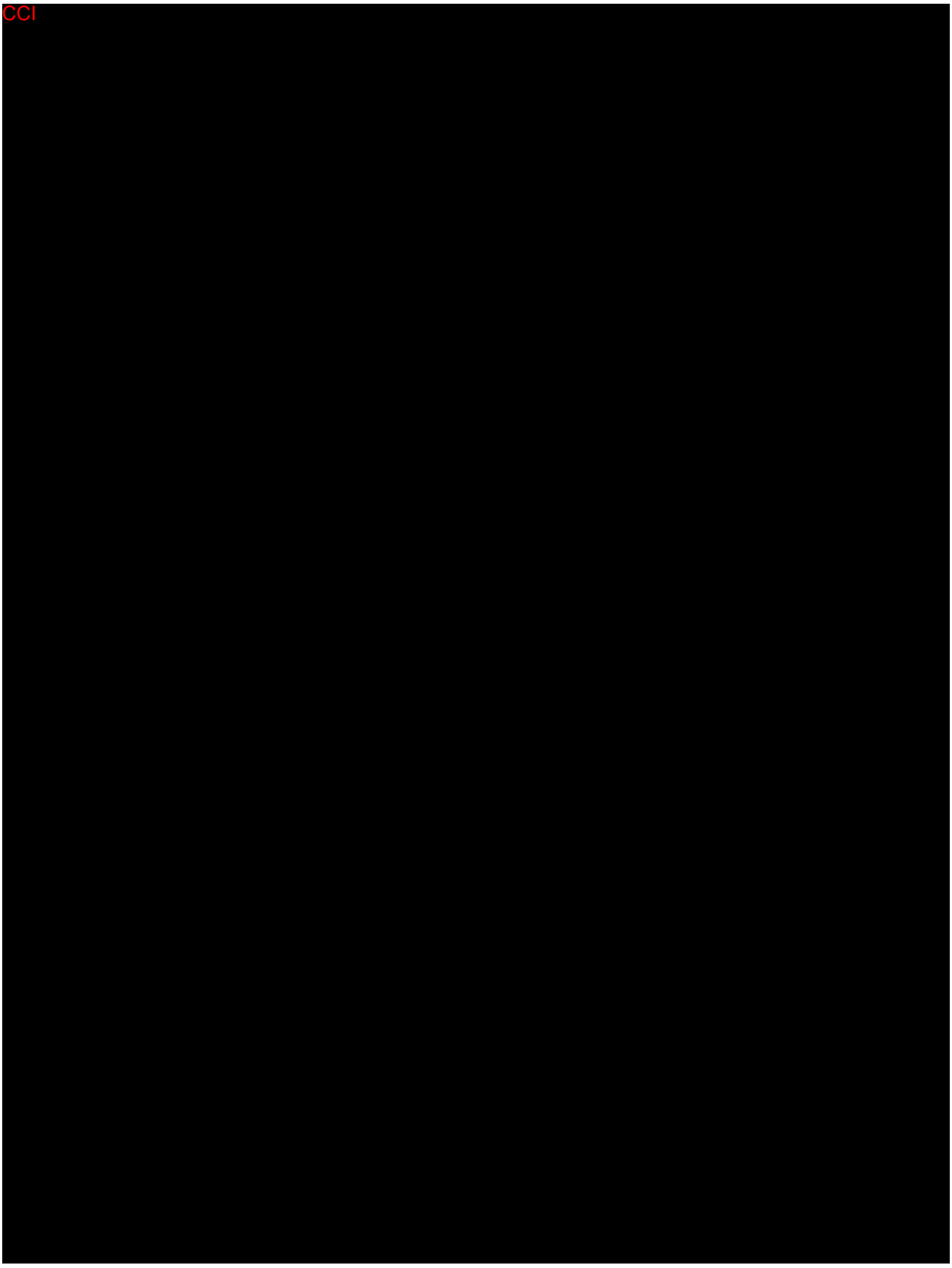
[redacted]

10.12. Appendix 12: CCI [redacted]

CCI [redacted]

10.13. Appendix 13: CCI

CCI



CCI

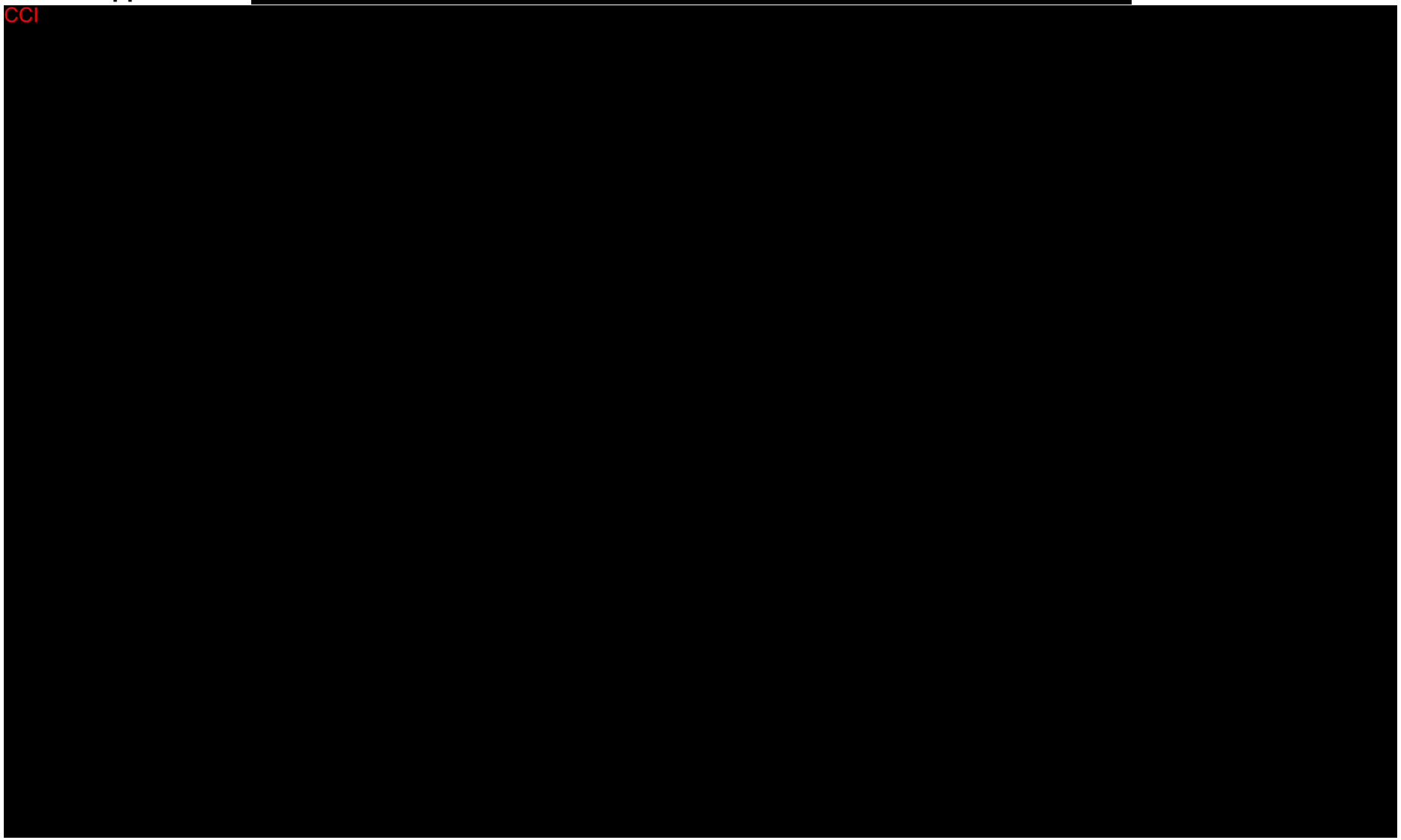
[redacted]

CCI

[redacted]

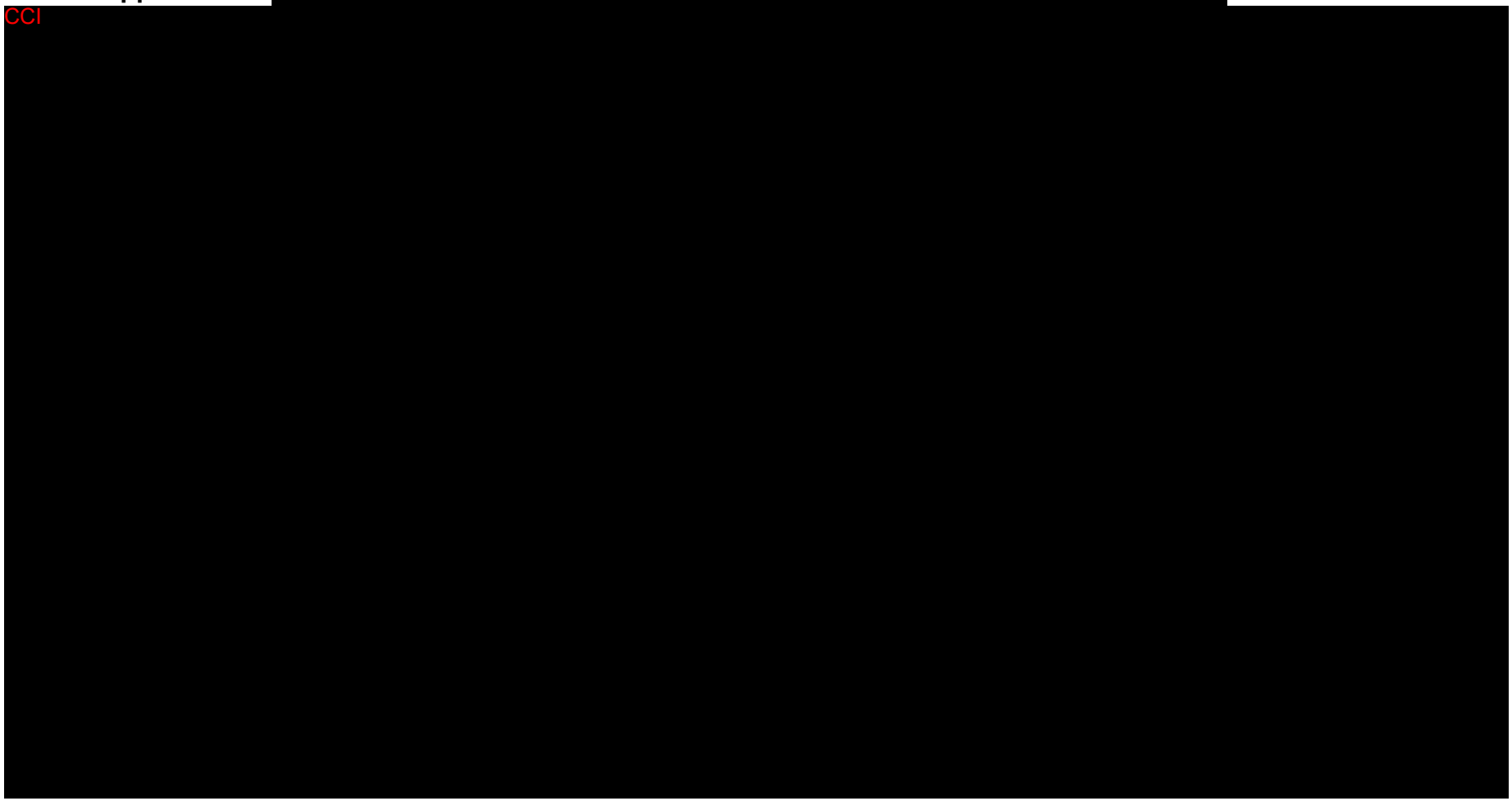
10.14. Appendix 14: CCI

CCI



10.15. Appendix 15: CCI

CCI



10.16. Appendix 16: Study Medication Acceptability and Palatability Assessment

Study Medication Tolerability – Caregiver Assessment

[NOTE: Text in bold explains which questions are asked when and to guide implementation on the eDevice in this protocol; they do not need to be translated.]
This tolerability assessment is used in pediatric clinical treatment trials. It is to be administered at the time point specified in the study protocol Time and Events Schedule. For studies using electronic COA assessments, this assessment should also be included in the eCOA implementation.

In general, how did the child react when he/she was given the medicine? (note all that apply)

- ☐ Child took medicine easily ***[cannot be checked if other options selected]***
- ☐ Disgusted expressions after tasting medicine
- ☐ Cried after tasting medicine
- ☐ Would not open mouth or turned head away to avoid medicine
- ☐ Spit out or coughed out medicine
- ☐ Gagged
- ☐ Vomited (within 2 minutes of swallowing medicine)

Thank you!

10.17. Appendix 17: RSV Symptom Onset to Randomization Calculator

The Symptom Onset to Randomization Calculator uses the 24-hour clock.

Day of 1st RSV sign/symptom onset	Time period of 1st RSV sign/symptom onset	Patient out of window for randomization
Saturday	Night (Sunday 00:00-05:59)	**≥ 6:00 Wednesday**
Sunday	Morning (06:00-11:59)	**≥ 12:00 Wednesday**
Sunday	Afternoon (12:00-17:59)	**≥ 18:00 Wednesday**
Sunday	Evening (18:00-23:59)	**≥ 00:00 Thursday**
Sunday	Night (Monday 00:00-05:59)	**≥ 6:00 Thursday**
Monday	Morning (06:00-11:59)	**≥ 12:00 Thursday**
Monday	Afternoon (12:00-17:59)	**≥ 18:00 Thursday**
Monday	Evening (18:00-23:59)	**≥ 00:00 Friday**
Monday	Night (Tuesday 00:00-05:59)	**≥ 6:00 Friday**
Tuesday	Morning (06:00-11:59)	**≥ 12:00 Friday**
Tuesday	Afternoon (12:00-17:59)	**≥ 18:00 Friday**
Tuesday	Evening (18:00-23:59)	**≥ 00:00 Saturday**
Tuesday	Night (Wednesday 00:00-05:59)	**≥ 6:00 Saturday**
Wednesday	Morning (06:00-11:59)	**≥ 12:00 Saturday**
Wednesday	Afternoon (12:00-17:59)	**≥ 18:00 Saturday**
Wednesday	Evening (18:00-23:59)	**≥ 00:00 Sunday**
Wednesday	Night (Thursday 00:00-05:59)	**≥ 6:00 Sunday**
Thursday	Morning (06:00-11:59)	**≥ 12:00 Sunday**
Thursday	Afternoon (12:00-17:59)	**≥ 18:00 Sunday**
Thursday	Evening (18:00-23:59)	**≥ 00:00 Monday**
Thursday	Night (Friday 00:00-05:59)	**≥ 6:00 Monday**
Friday	Morning (06:00-11:59)	**≥ 12:00 Monday**
Friday	Afternoon (12:00-17:59)	**≥ 18:00 Monday**
Friday	Evening (18:00-23:59)	**≥ 00:00 Tuesday**
Friday	Night (Saturday 00:00-05:59)	**≥ 6:00 Tuesday**
Saturday	Morning (06:00-11:59)	**≥ 12:00 Tuesday**
Saturday	Afternoon (12:00-17:59)	**≥ 18:00 Tuesday**
Saturday	Evening (18:00-23:59)	**≥ 00:00 Wednesday**

10.18. Appendix 18: List and Definition/Diagnostic Criteria of Assessed RSV-related Complications

AEs occurring after study intervention initiation as reported by investigators with the following terms:

Note: The diagnostic criteria are provided as guidance in the diagnostic process.[43]

Respiratory complications:

- Respiratory failure: Either hypoxemic respiratory failure characterized by an arterial oxygen tension (PaO_2) 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.

  Diagnostic criteria: PaO_2 <60 mmHg with a normal or low $PaCO_2$, or $PaCO_2$ >50 mmHg.

- Apnoeic attacks: Cessation of breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia (<100 beats per minute), cyanosis, or pallor.

  Diagnostic criteria: Clinical observation or report or biosensor recording of respiratory rate and heart rate.

- Bronchiolitis: An acute inflammatory injury of the bronchioles that is usually caused by a viral infection and characterized by[18]

  a) preceding viral upper respiratory tract infection, cough and/or rhinorrhea

  b) exposure to an individual with viral upper respiratory tract infection

  c) signs of respiratory illness may also include: Tachypnea, intercostal and/or subcostal retractions, accessory muscle use, nasal flaring, grunting, color change or apnea, wheezing or crackles, and/or lower O_2 saturations.

  Diagnostic criteria: Clinical evaluation with findings of tachypnea, intercostal and/or subcostal retractions, accessory muscle use, nasal flaring, grunting, color change or apnea, wheezing or crackles, and/or O_2 saturation <96% (measured by oximeter).

- Bronchial obstruction: Anatomic narrowing or occlusion of bronchioles, resulting in a decreased ability to move air and characterized by an abnormal forced expiratory volume in the first second of expiration and its ratio to forced vital capacity (FEV1/FVC) is <80%).[7]

  Diagnostic criteria: Spirometry with FEV1/FVC <80%; oscillometry.

- Pneumonia: An invasion of the lower respiratory tract, below the larynx by pathogens either by inhalation, aspiration, respiratory epithelium invasion, or hematogenous spread. Neonates are at risk for bacterial pathogens present in the birth canal. Pneumonia is characterized by observation of signs of respiratory distress, including tachypnea, nasal flaring, lower chest in-drawing, or hypoxia on room air.[13]

  Diagnostic criteria: Clinical evaluation; tachypnea (≥60 breaths in a child aged <2 months; ≥50 breaths/min in a child aged 2 11 months; ≥40 breaths/min in a child aged 1 5 years); O_2 saturation <96% (measured by oximeter); chest auscultation findings (decreased breath sounds, bronchial breath sounds, crackles, abnormal vocal resonance, or pleural rub); chest X-ray with airspace opacity, lobar consolidation, or interstitial opacities.

- Asthmatic crisis: Common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation.

  Diagnostic criteria: Clinical evaluation with wheezing on expiration (on auscultation or audible), prolonged expiration, resonant percussion note, hyperinflated chest, rhonchi on auscultation, lower chest wall in-drawing if severe; improvement on use of bronchodilators.

Infectious complications:

- Otitis media: Infection of the middle ear space. It is a spectrum of diseases that include acute otitis media (AOM), chronic suppurative otitis media (CSOM), and otitis media with effusion (OME), caused by viral, bacterial, or coinfection. Fever, otalgia, headache, irritability, cough, rhinitis, listlessness, anorexia, vomiting, diarrhea, and pulling at the ears are common, but nonspecific symptoms.[9]

  Diagnostic criteria: (Pneumatic) otoscopy: detection of middle ear effusion.

- Bacterial respiratory tract infections: Self-limited irritation and swelling of the upper airways, caused by bacteria, with associated cough with no proof of pneumonia, lacking a separate condition to account for the patient symptoms, or with no history of emphysema/chronic bronchitis.

  Diagnostic criteria: Clinical evaluation; sputum culture with identification of bacterial pathogens.

- Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection and characterized by presence of acute fever (>39 °C) and severe illness when no other cause is found.[34]

  Diagnostic criteria: Acute fever (>39 °C); blood culture with identification of bacterial pathogens; clinical picture of shock (lethargy, tachypnea, cold, skin, prolonged [>3 seconds] capillary refill, fast weak pulse, and sometimes low blood pressure).

Cardiovascular complications:

- Arrhythmia: Absence or disruption of cardiac electrical activity resulting in abnormality in the heart's normal rhythmic pattern and characterized by presentation to the emergency department with symptoms of palpitations, fatigue and/or syncope.[21]

  Diagnostic criteria: ECG findings; irregular pulse.

- Cardiogenic shock: Primary cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion.

  Diagnostic criteria: Systolic blood pressure ≤90 mm Hg for ≥30 minutes or support to maintain systolic blood pressure ≥90 mm Hg; urine output ≤30 mL/hr or cool extremities.

- Hemodynamic instability: Defined as perfusion failure, represented by clinical features of circulatory shock and advanced heart failure and characterized by hypotension, abnormal heart rates, cold extremities, peripheral cyanosis, and mottling together with bedside measurements of right-sided filling pressure and decreased urine flow.[41]

  Diagnostic criteria: Clinical evaluation; BP and HR measurements abnormal for age of participant.

- Congestive cardiac failure: Complex clinical syndrome that results from any functional or structural heart disorder, impairing ventricular filling or ejection of blood to the systemic circulation to meet the systemic needs. It is caused by diseases of the endocardium, myocardium, pericardium, heart valves, vessels or metabolic disorders. Congestive cardiac failure is characterized by difficulty in feeding (from prolonged feeding time intake to frank intolerance), cyanosis, tachypnea, sinus tachycardia, and diaphoresis.[33]

  Diagnostic criteria: Clinical evaluation; tachypnea (≥60 breaths in a child aged <2 months; ≥50 breaths/min in a child aged 2 11 months; ≥40 breaths/min in a child aged 1 5 years); tachycardia (heart rate >160/min in a child <12 months; >120/min in a child aged 12 months to 5 years).

Acid-base or electrolyte complications:

- Metabolic acidosis (serum HCO_3 <16): Disturbances in the homeostasis of plasma acidity which is characterized by increase hydrogen ion concentration in the systemic circulation.
- Metabolic alkalosis (serum HCO_3 >30): Defined as a disease state where the body's pH is elevated to greater than 7.45 secondary to some metabolic process.
- Hyponatremia (Na^+ <130 mEq/L).
- Hypokalemia (K^+ <2.9 mEq/L).
- Hyperkalemia (K^+ >6.0 mEq/L).
- Hypocalcemia (Ca^{2+} <7.7 mg/dL or equivalent to Grade 2 in children ≤3 months).
- Hypercalcemia (Ca^{2+} >11.9 mg/dL or equivalent to Grade 2 in children ≤3 months).
- Hypoglycemia (glucose <54 mg/dL).
- Hyperglycemia (glucose >160 mg/dL).

  Diagnostic criteria: Laboratory values outside of the values above if considered clinically significant.

10.19. Appendix 19: Guidance on Study Conduct during the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic 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 will be 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, the participant's parent(s)/caregiver(s) will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. The participant's parent(s)/caregiver(s) 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 after consultation between the participant's parent(s)/caregiver(s) and 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 case report form (CRF).

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 during the treatment period and in case the participant's safety is considered to be at risk, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Additional follow-up and management of a laboratory-confirmed SARS-CoV-2-infected participant will be per local standard-of-care, independent to the study visits. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

There are no available data suggesting additional risk to participants in rilematovir clinical studies caused by locally approved (including emergency use-authorized) COVID-19 vaccines or an interaction between COVID-19 vaccines and rilematovir. Local package inserts for COVID-19 vaccines, including contra-indications, must be followed as well as local vaccination guidelines.

For participants with signs and symptoms of febrile illness or acute infection, it is recommended that administration of COVID-19 vaccines be timed to occur after study completion or at least 2 weeks after the last dose of study intervention so that signs and symptoms can be clearly attributed to RSV infection or vaccination. In case a participant received a COVID-19 vaccine during study period, the COVID-19 vaccine must be documented on the concomitant therapy page of the eCRF.

Investigators should make an assessment of the relatedness of any AE reported following COVID-19 vaccination to study intervention, the underlying RSV infection and/or COVID-19 vaccine (as described in Section 10.4.2). If the event is serious and considered related to both the COVID-19 vaccine and the study intervention, it is to be recorded as a serious adverse reaction (as described in Sections 8.3.4 and 10.4.5). Adverse events expectedness is described in Section 10.4.1.

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.
- 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 videoconference, eg, Facetime, Skype, 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. These virtual assessments include review of AEs, concomitant medications, monitoring of ObsRO Signs/Symptoms, ObsRO GHQ, and Caregiver Impact Questions completion and medical resource utilization, and review of parent(s)/caregiver(s) responses to the ObsRO GHQ. 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 MT swab can be stored at home and picked up by study site personnel or courier.
  - In case home visits cannot be performed, nasal MT swabs, if required as per the Schedule of Activities, may be collected by the parent(s)/caregiver(s). Training and written instructions to collect the nasal MT swab will be provided to the parent(s)/caregiver(s).
- 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.
  - If both caregivers need to provide consent per local regulations, the sponsor allows obtaining the second consent remotely (phone or video) if allowed per local guidance. In all cases, the written main ICF will be obtained prior to any study-specific assessments.

10.20. Appendix 20: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	This document
Original Protocol	17 August 2020

11. REFERENCES

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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

Signature: [electronic signature appended at the end of the protocol] Date: _____

(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.

Signature

User	Date	Reason
PPD	04-May-2021 09:40:37 (GMT)	Document Approval