Janssen Research & Development*

Statistical Analysis Plan

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

JNJ-53718678 (rilematovir)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	07 April 2022	Not Applicable	Initial release
2	24 May 2022	Table 3. Visit Windows. Footnote was updated.	Visit windows to be considered for each PRESORS information presentation, were clarified.
		In Section 5.4.2.1. Definitions of the Supportive Secondary Endpoints, the rationale for deriving only the summary parameter Key RSV signs/symptoms for ObsRO and ClinRO is provided. The related Sections 5.4.2.1.1, 5.4.2.1.2 and 5.4.2.2.1 have been updated accordingly.	Due to an error with ObsRO v9.0 instructions following questions related to cough item, caregivers may inadvertently skipped the question related to feeding problems, and data for this item may not be available.
		Table 6. Key Secondary Endpoints. The approximate 24h resolution of the Key RSV signs/symptoms for the endpoint time to resolution of Key RSV signs/symptoms after free of supplementation for at least 24h, was added. Censoring rules were updated.	The definition of the resolution of Key RSV signs/symptoms in this time to event endpoint is different than when defined by study day. Censoring rules were updated since PRESORS are meant to be collected up to Day 21(~ 504h) rather than until Day 35 (~ 840h).
		Table 7. Parameters based on ObsRO. Number of caregivers was removed. Table 8. Parameters based on ClinRO. Number of clinicians was removed. Summaries planned were removed from section 5.4.2.2.1.	Due to an error in data collection, the number of different caregivers and clinicians per participant will not be summarized.
		Table 8. Parameters based on ClinRO. The resolution categories for signs/symptoms and summary parameters were clarified.	The categories to be considered are resolved, not resolved and not available.
		Table 9. Additional Clinical Course Parameters. The set of participants for which duration of ICU stay and supplemental feeding/ hydration will be provided, was corrected.	Duration will be provided irrespective whether a participant did have any stay/use prior to first dose of study intervention.
		Section 5.6.2.1 Clinical Laboratory Test. For children younger than or aged 3 months, a correction was noted to DMID table for calcium toxicity ranges.	The correction was implemented in a protocol amendment as a note to the DMID table but due to early termination of the trial, the amendment was never submitted.
		The Table 14. ECG abnormalities was adjusted.	Table amended to clarify that abnormalities for QTC formula are for both QTcF and QTcB.
		Section 5.7.2 Pharmacokinetics. No descriptive summary of rilematovir concentrations needed.	Only listing to be provided.
		Some adjustments were performed to Section 6.10 Appendix 10 Missing Data.	Additional scenarios needed to be foreseen to impute missing dates/times.

SAP Version	Approval Date	Change	Rationale
		Section 6.13 Appendix 13 Clinician PRESORS ClinRO, concept "Tachycardia".	Derivation for Tachycardia corrected since based on ClinRO questions 4 and 8.

1. INTRODUCTION

Rilematovir is an investigational respiratory syncytial virus (RSV) specific fusion inhibitor belonging to the indole chemical class and under development for the treatment of RSV infection.

The Phase 3 DAISY study protocol (53718678RSV3001) is based on the interim analysis (IA) results (data cut-off 02 January 2020) of the hospitalized cohort (Cohort 1), of the ongoing Phase 2 CROCuS study (53718678RSV2002). The most recent IA results of the completed hospitalized cohort (final database lock date 08 June 2021) in CROCuS, confirmed that rilematovir is safe and well-tolerated and no safety signals were observed. The benefit-risk balance remained positive, thus supporting continuation of the DAISY study. However, the CROCuS completed hospitalized cohort IA results showed a smaller treatment effect of rilematovir versus placebo on the RSV Recovery Scale (RRS) compared to the effect observed in the previous interim analysis.

In December 2021 the Sponsor informed investigators about the new IA results and additional exploratory analyses performed that led to the Sponsor's intention to amend the Phase 3 DAISY study into a Phase 2 study. However, on 25 February 2022 the Sponsor decided to focus the immediate efforts on the non-hospitalized RSV (pediatric and adult) population and terminate the DAISY study. At the time the decision for study termination was taken, 28 participants had been enrolled in the study of whom 3 were ongoing and allowed to complete the study through study Day 35. The sub-study in neonates had not been initiated therefore, no neonates had been enrolled in the DAISY study.

In light of the early termination of the study, this Statistical Analysis Plan (SAP) (based on the developed draft version) contains definitions of analysis sets, derived variables and statistical methods for the DAISY study including safety and limited efficacy. The SAP is to be interpreted in conjunction with the protocol.
This SAP covers the final analysis that will be performed when all randomized participants have completed Day 35 or discontinued earlier. Due to termination of the study, no Independent Data Monitoring Committee (IDMC) review nor analyses will be performed.

If appropriate, psychometric validation analysis plans for the Pediatric RSV Electronic Severity and Outcomes Rating Systems Caregiver (ObsRO) and Clinician (ClinRO) questionnaires will be described in a separate Psychometric Analysis Plan (PAP).

1.1. 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 day when at least 50% of the participants across treatment arms are discharged from the hospital (the day for the RRS evaluation will be determined based on blinded data at the first interim analysis by an independent statistician).
Secondary	
Key Efficacy	
• To evaluate the superiority of rilematovir compared to placebo	• Proportion of participants clinically resolved from RSV disease based on Clinician Rated Outcome

Objectives	Endpoints
treatment with respect to clinical resolution of RSV disease.	(ClinRO) Signs/Symptoms[c,e] as assessed on the same 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 Rated 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 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.
Supportive Efficacy	
• 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.

Objectives	Endpoints
	• 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 (as evaluated by the investigator). • 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 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.
Safety	
• 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.

Objectives	Endpoints
Pharmacokinetics	
• 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.
Other	
• To evaluate the acceptability and palatability of the rilematovir formulation.	• Acceptability and palatability of the rilematovir formulation as assessed through a questionnaire.
• 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.
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). • 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.	• 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 5.3.1.

Objectives	Endpoints
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 no medical need for ICU, AND Key RSV Signs/Symptoms resolved to absent or mild as per the ClinRO Signs/Symptoms (see Section 5.4.1).[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	
e. See protocol Section 10.13 Appendix 13 and Section 10.14, Appendix 14 for definitions of resolved/not resolved.	
f. See Section 5.4.1 for the list of complications assessed.	

Given the limited number of participants enrolled in the study, the analyses will be restricted to the following endpoints. No hypothesis is tested nor estimands will be derived.

Efficacy:

- **Primary endpoint:** RRS as assessed from baseline to Day 8.
- **Key secondary endpoints:**
  - clinically resolved from RSV disease based on Clinician Rated Outcome (ClinRO) Signs/Symptoms as assessed from baseline to Day 8.
  - Time from first study dose to resolution of Key RSV signs/symptoms based on parent's/caregiver's Observer Rated Outcome (ObsRO) Signs/Symptoms and supplementation free (oxygen and feeding/hydration) for at least 24 hours.
  - Incidence in post-baseline RSV-related complications.
- **Supportive secondary endpoints:**
  - Viral Load
    - 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.
  - Duration of hospitalization, ICU stay, and of any type of supplementation (oxygen and/or feeding/hydration).
  - Number and type of medical encounters.
  - Incidence of use of concomitant medications.
  - Pediatric RSV Electronic Severity and Outcome Rating Systems (PRESORS)
    - Proportion of participants with signs/symptoms of RSV disease resolved/not resolved over time, based on ObsRO and ClinRO separately.

- **Other secondary endpoints:**
  - Acceptability and palatability of the rilematovir formulation as assessed through a questionnaire.
  - Sequence changes (post-baseline) in the RSV F gene compared to baseline.

Safety

Safety and tolerability, as assessed by adverse events (AEs), clinical laboratory testing, electrocardiograms (ECGs), vital signs throughout the study.

Pharmacokinetics (PK)

Rilematovir PK concentrations.

1.2. Study 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 IA#1 results of the main study. The main study will be opened for enrollment of neonates at all sites following completion of the substudy in neonates and IDMC positive recommendation. This SAP only describes the analyses to be performed in the main study.

Participants with RSV disease (ie, diagnosed with 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) will be enrolled.

Approximately 737 hospitalized RSV-infected 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 SOC sample used for local RSV diagnosis, whichever comes first, and no later than 3 days after onset of first RSV sign/symptom.

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) and by region (Asia-Oceania, EMEA, Northern America, and Latin America-The Caribbean)[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 1). Study intervention (oral suspension) will be administered orally, bid, with a treatment duration of 7 days (14 consecutive doses).

Table 1: 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 protocol 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. For neonates (Age Group 4), the eq. 20 mg/mL JNJ-53718678-AAA oral suspension is diluted with an appropriate volume of solvent for oral suspension to an equivalent 5 mg/mL JNJ-53718678-AAA oral suspension (containing 5.75 mg/mL JNJ-53718678-ZCL, the hemi-tartrate of JNJ-53718678-AAA). 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 participants ≥28 days to ≤5 years of age and observed for the 250 mg bid regimen in adults.

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 (SoA) accordingly defined in the protocol. If a participant is re-hospitalized after discharged due to worsening of RSV disease during the treatment period, administration of study intervention in the bid regimen should continue.

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.

2. STATISTICAL HYPOTHESES

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.

Due to early termination of the study, the RRS will be derived from baseline to Day 8, but no formal hypothesis testing will be performed.

3. SAMPLE SIZE DETERMINATION

Please see protocol Section 9.2 Sample Size Determination.

At the time of study termination, 28 participants were randomized and treated.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	**Description**
Enrolled	All participants who signed the main ICF.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Intent-to-Treat infected set (ITT-i)	ITTI-i includes all randomized participants who received at least 1 dose of study intervention and had an RSV infection confirmed* by central laboratory analysis. Participants with confirmed SARS-CoV-2 infection (positive test by central laboratory analysis up to day 14) are excluded. *A participant is considered to have a centrally confirmed RSV infection based on the RSV RT-qPCR assay if he/she has: • a positive RSV RT-qPCR result from central lab at baseline or • two positive RSV RT-qPCR results from central lab post-baseline up to Day 6 This population will be used for the analysis of efficacy endpoints, as randomized.
Safety	The safety analysis set includes all participants who received at least 1 dose of study intervention. This population will be used for the analysis of safety endpoints, as treated.
Pharmacokinetics analysis set (PKAS)	PKAS includes participants who have received at least 1 dose of rilematovir and have at least 1 valid blood sample drawn for PK analysis.

5. STATISTICAL ANALYSES

5.1. General Considerations

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.2 (or higher).

Phases will be constructed as defined in Table 2.

Table 2: Analysis Phases

Analysis Phase [number]	Start Date/Time	End Date/Time
Pre-Screening [0]		23:59 of the date before signing main informed consent form*
Screening [1]	00:00 of the date of signing the informed consent form *	1 minute before the first bid dose study intervention administration in the trial
Intervention [2]	Date/time of first bid dose study intervention administration in the trial	23:59 of the last day of study intervention administration + 3 days or 23:59 of the cut-off date for the IA, or 23:59 of the date of trial termination, whichever comes first
Follow-up [3]	1 minute after the End of Intervention Phase	23:59 of the day of trial termination (date of last contact) or 23:59 of the cut-off date for the IA, whichever comes first

* For some sites, diagnostic ICF (Dx ICF) is required if RSV infection testing is not part of SOC or the SOC RSV diagnostic assay is not approved for use in the study. The earliest date between Dx ICF and main ICF will be used as a reference for viral load sample to be considered. Screening only starts once main ICF signed.

Assessments will be assigned to phases based on their date/time, but seconds will be ignored overall. If the day part of the start date of the assessment is present but the time part is missing, the assessment will be treated as if it started at 00:00 on the day of the event (unless for Adverse Events see Section 5.6.2). If the day part of the end date of the assessment is present but the time part is missing, the assessment will be treated as if it happened at 23:59 on the day of the event. No formal imputation will be done, these rules will only be applied to allocate assessments to phases.

5.1.1. Pre-Screening

In order to better explore the impact of any medical encounter from time of presentation at the hospital/clinic up to signing the main ICF on RSV baseline characteristics, the following information will additionally be collected in the eCRF as much as possible if available.

- At presentation and between presentation and prior to screening for:
  - Clinical evaluation: vital signs assessments, respiratory rate, heart/pulse rate, body temperature, and SpO_2.
  - Key RSV signs/symptoms breathing problems (nasal flaring, head bobbing, grunting), retractions, tachypnea, wheezing, cough, and tachycardia.
- Complete physical examination as to be performed at screening.

Please notice that information collected from presentation to the Hospital/Clinic and prior to study (main) informed consent signed, may be included in summaries but not considered in the

derivation of any screening nor baseline result. The data may be used to conduct exploratory economic analyses.

5.1.2. Baseline

In general, the baseline record is defined as the last record before the first intake of the study drug, except for the following assessments:

- **RSV RNA viral load (VL):**
  - Last available assessment within the 24 hours (h) prior to or at the same time of first drug intake will be considered as baseline.
  - If no assessment within the 24h prior to or at the same time of first drug intake, but there is a result available no later than 1h post first study drug intake, the baseline assessment will be the first assessment completed within 1h post first drug intake.
  - If none of the above assessments are available, but there is an assessment available before the 24h prior to first drug intake, it will be considered as baseline.
- **PRESORS:**
  - Last available assessment within the 8h prior to first drug intake.
  - If no assessment is available within 8h prior to first drug intake, but there is an assessment completed within 1h post first drug intake, then baseline assessment will be the assessment completed within 1h post first drug intake.
  - If none of the above assessments are available, but there is an assessment available before the 8h prior to first drug intake, it will be considered as baseline.

5.1.3. Relative Day

Study Day 1 is the reference day and defined as the date of first study medication intake (there is no 'Day 0'). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

- The relative day for visits **before Day 1** will be defined as:

$$\textit{Relative day} = \textit{visit date} - \textit{reference date}$$

- The relative day for visits **on or after Day 1** will be defined as:

$$\textit{Relative day} = \textit{visit date} - \textit{reference date} + 1$$

5.1.4. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1.

- If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints.
- If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.
- If there are two measurements on the same date and time, then the measurement with the highest sequence number will be used.

Exceptions to the general rule:

- **RSV RNA viral load**

  For the analyses of VL (scheduled once daily), if multiple nasal swabs were taken on a single day, the above rules will only be applied after having determined the maximum viral load per day. The maximum viral load on a day will be used for windowing. Please notice that baseline viral load follows the rules described in Section 5.1.2.

- **Electrocardiogram (ECG)**

  For Day 1 and Day 3, the 1h post-dose assessment is targeted. The dose to be considered as reference for each day is as follows:

  – Day 1, 1h post-dose ECG will be after first dose of study intervention.

  – Day 3, 1h post-dose after the last administered dose of study intervention prior to the on-site visit. This means, the study dose intervention that is closer to ECG reading on the target day

  On these days, an additional time window of 45-90 minutes post-dose was identified in the protocol. The upper bound of the ECG window is expanded up to 120 minutes to be aligned with the lower bound of 45 minutes. This was deemed acceptable as plasma concentrations, which are the driver behind a possible QTc prolongation, at 120 minutes are similar to plasma concentrations at 45 minutes. Therefore, the time window to be applied in the analysis on Day 1 and Day 3 is 45-120 minutes, and the result to be considered is as follows:

  – If an ECG recording is available within the target day and after first administration within the time window indicated, it will be used for the analysis 1h post-dose.

  – If one or more ECG recordings are available within the target day and within the time window, the closest one to target time will be used in the analysis.

  – If ECG recording (s) is available within the target day but outside time window indicated, it will not be used for any 1h post-dose analysis rather for the general analysis for that day where general rules for visit windows will be applied.

Once baseline is assigned, any assessment performed prior to the defined baseline, will be assigned to Screening. Screening visits will not be used in summary tables, only in listings.

Any assessment performed after first drug intake not considered baseline but within Day 1, will be assigned to Day 1, post-dose. Visit windows for VL and ECG/labs are defined as in Table 3.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 3) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 3: Visit Windows

Parameter	Scheduled Visit Number	Time Interval (Label on output)	Time Interval (Day)*		Target Time Point (Day)
			During hospitalization	After Discharge+	
Viral Load (VL)	0	Baseline	[<=1] $	[<=1] $	[1]
	1	Day 1	[1]	[1]	[1]
	2	Day 2	[2]	[2]	[2]
	3	Day 3	[3]	[3]	[3]
	4	Day 4	[4]		[4]
	5	Day 5	[5]	[4-7]	[5]
	6	Day 6	[6]		[6]
	7	Day 7	[7]		[7]
	8	Day 8	[8-11]	[8-11]	[8]
	14	Day 14	[12-17]	[12-17]	[14]
	21	Day 21	[18-+∞]	[18-+∞]	[21]
Clinical Evaluation SBP & DBP	0	Baseline	[<=1] $	[<=1] $	[1]
	1	Day 1	[1]	[1]	[1]
	2	Day 2	[2]	[2]	[2]
	3	Day 3	[3]	[3]	[3]
	4	Day 4	[4]		[4]
	5	Day 5	[5]	[4-7]	[5]
	6	Day 6	[6]		[6]
	7	Day 7	[7]		[7]
	8	Day 8	[8]	[8-11]	[8]
	9	Day 9	[9]		[9]
	10	Day 10	[10]		[10]
	11	Day 11	[11]		[11]
	12	Day 12	[12]		[12]
	13	Day 13	[13]		[13]
	14	Day 14	[14]	[12-17]	[14]
	15	Day 15	[15]		[15]
	16	Day 16	[16]		[16]
	17	Day 17	[17]		[17]
	18	Day 18	[18]		[18]
	19	Day 19	[19]		[19]
	20	Day 20	[20]		[20]
	21	Day 21	[18-29]	[18-29]	[21]
	35	Day 35	[30-+∞]	[30-+∞]	[35]
ECGs	0	Baseline	[<=1] $		[1]
	1	Day 1	[1] #		[1]
	3	Day 3	[2-5] #		[3]
	8	Day 8	[6-11]		[8]
	21	Day 21	[12-29]		[21]
	35	Day 35	[30-+∞]		[35]
Safety laboratory	0	Baseline	[<=1] $		[1]
	8	Day 8	[1-11]		[8]
	21	Day 21	[12-29]		[21]

Table 3: Visit Windows

Parameter	Scheduled Visit Number	Time Interval (Label on output)	Time Interval (Day)*		Target Time Point (Day)
			During hospitalization	After Discharge+	
	35	Day 35	[30-+∞]		[35]

*Relative to Study Day 1[$] Baseline is defined as the last measurement before first study drug intake. Please also see Section 5.1.2.
Additionally, on Day 1 and Day 3, the 1h post dose assessment is targeted with a time window of 45-120 minutes from study intervention dose. Please see Section 5.1.4.
+ The earliest timepoint when a participant can be discharged is Day 2. Afterwards limited on-site visits required. For summary tables and figures, visit information as per "after discharge" will be presented. For listings, all information will be presented.
Due to early termination of the study, PRESORS ObsRO/ClinRO information will be provided for each study day irrespective of hospitalization status. To evaluate the missing ClinRO assessments, the visit windows as defined in the protocol will be applied.

Visits that occurred outside the windows allocated in the above table (ie. visits not being performed per protocol), may be assigned a window for consistency (based on the relative day). However, these visits will not be used in summary tables and figures but will only be shown in individual listings and figures.

Table 4: Planned Collection of PRESORS (ClinRO, ObsRO), Clinical Evaluation and Blood Pressure

Assessments	During Hospitalization	After Discharge
Clinical Evaluation[£]	BID from Day 1 to Day 14 and QD from Day 15 to Day 21 + Day 35*	QD once at clinic visits (Day 3,5,8,14 and 21) + Day 35*
SBP & DBP		
PRESORS ClinRO	BID from Day 1 to Day 14 and QD from Day 15 to Day 21	QD once at clinic visits (Day 3,5,8,14* and 21)
PRESORS ObsRO	BID from Day 1 to Day 14 and QD from Day 15 to Day 21	

[£] Respiratory rate (RR), Heart/pulse rate, Temperature, SpO_2.
* Only in case of on-site visit.

Table 5: Time Slot in a Day for BID days

Slot of the Day	Time
Morning	00:00– 11:59
Evening	12:00 – 23:59

In case of BID assessments, the worst value per day will be presented for the daily summaries unless otherwise specified.

5.1.5. Data Handling Rules for RSV RNA Viral Load

For analysis purposes, the log_{10} qRT-PCR viral load will be imputed with the midpoint on the log scale between the limit of detection (LOD) and lower limit of quantification (LLOQ) of the RSV qRT-PCR assay when the result is 'target detected' (TD) but non-quantifiable.

- For the RSV-A qRT-PCR assay, the LOD is 620 copies/mL and the LLOQ is 1000 copies/mL, a result that is TD will be imputed with 2.90 $\log_{10}$ copies/mL.
- For the RSV-B qRT-PCR assay, the LOD is 80 copies/mL and the LLOQ is 250 copies/mL, a result that is TD will be imputed with 2.15 $\log_{10}$ copies/mL.

When the result is 'target not detected' (TND) (ie., below the LOD), for both RSV A and RSV B the value of TND will be imputed with 0 $\log_{10}$ copies/mL.

For the overall analysis of viral load, all the viral load results of the RSV type with which the participant has been infected will be used.

In case of co-infection with both subtypes RSV A and B, the rules below will be applied for the overall analyses of viral load from the time the co-infection is detected (ie. result of TD or >LLOQ):

- In case of two quantifiable results: the $\log_{10}$ of the sum of the RSV A and RSV B results in copies/mL will be used.
- In case of a quantifiable result and a TD/TND result: use the imputed TD/TND on the copies/mL scale value and then use the $\log_{10}$ of the sum of the imputed value and the quantifiable result.
- In case of two TD results, or one TD and one TND result: use the imputed TD/TND on the copies/mL scale values and then use the $\log_{10}$ of the sum of the imputed values.
- In case of two TND results: impute as 0 log10.

If RNAse P = Not Detected AND RSV A = Not Detected AND RSV B = Not Detected sample will be excluded from the analysis.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be listed.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention (SAF)
- Participants randomized who received study intervention
- Participants in the ITT-i
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who discontinued study
- Reasons for discontinuation of study
- Participants who completed the study

The planned study intervention will be shown except for the SAF where the actual study intervention will be shown.

A listing of participants will be provided for the following category[ies]:

- Participants who were unblinded during the study period
- Participants who were excluded from ITT-I due to either RSV positive not confirmed and/or SARS-CoV-2 positive by central lab

Please notice that the above listing will not be provided if no cases occurred.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The RRS is an ordinal scale assessing a participant's clinical status. Each of the categories is based on data collected rather than asking the investigator to select the category in which the participant is every day.

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

RSV Recovery Scale (RRS)	
Order	**STATUS**
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 6.12).
**Mechanical ventilation includes both invasive and non-invasive mechanical ventilation.

Please see protocol Section 8.1.1.1 RSV Recovery Scale Assessments for the protocol defined RRS 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).

Due to early termination of the study, the RRS will be derived based on the actual worst status within a study day.

In case of missing ObsRO after the participant discharged from the hospital for the RRS categories/status 1 or 2, a two-step approach will be applied:

- **Step 1→** if ObsRO is missing in between two days on which ObsRO is available, then it will be imputed as indicated in the table below:

Previous Study Day Available ObsRO	Next Study Day Available ObsRO	Imputed value	RRS Category/Status
Resolved	Resolved	Resolved	1- Not Hospitalized without Signs/Symptoms
Not resolved	Not resolved	Not resolved	2- Not Hospitalized with Signs/Symptoms
Resolved	Not resolved	Not resolved	2- Not Hospitalized with Signs/Symptoms
Not resolved	Resolved	Not resolved	2- Not Hospitalized with Signs/Symptoms

- **Step 2→** in any other situation, the worst-case scenario of the 2 home categories of the RRS will be selected, ie "Not Hospitalized with Signs/Symptoms".

See Sections 6.10 and 6.11 for further details of the RRS categories derivations.

5.3.2. Estimand

Please see protocol Section 9.4.2.1.1 Estimand.

Due to early termination of the study, primary estimand will not be derived.

5.3.3. Analysis Methods

A summary of the proportions for each RRS category from baseline to Day 8 will be provided by intervention group.

Graphical displays and tabulations will be provided showing the proportion of participants per the RRS category and study day.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Secondary Endpoint(s)

Please see protocol Section 9.4.2 Efficacy Analyses.

Due to early termination of the study, only 3 out of the 5 original key secondary endpoints will be derived (please see Section 1.1). The estimands for each of these 3 endpoints are not defined and formal testing will not be performed.

1. Proportion of participants clinically resolved from RSV disease based on Clinician Rated Outcome (ClinRO) signs/symptoms.

2. Time from first dose of study intervention to first resolution of Key RSV Signs/Symptoms based on parent's/caregiver's Observer Rated Outcome (ObsRO) Signs/Symptoms and supplementation free for at least 24 hours.

3. RSV related complication with onset after study intervention initiation.

5.4.1.1. Definition of Endpoint(s)

Table 6: Key Secondary Endpoints

Measurement	Formula
Clinically Resolved	A participant will be considered as clinically resolved at study day if based on actual information there is: • No need of oxygen supplementation • No need of supplemental feeding/hydration • No need of ICU AND • Resolution of Key RSV Signs/Symptoms based on ClinRO (please see Section 6.13) Please notice that as for the RRS, actual episodes of supplementation and ICU stay are considered. Key RSV Signs/Symptoms resolution based on ClinRO occurs when all signs/symptoms reach "resolved" status at the study day (please see **resolution definition** in Table 8). Since the PRESORS ClinRO is not assessed on a daily basis once participant is discharged from the hospital (only assessed during post-discharge follow-up visits to the site), if no PRESORS ClinRO available on a specific study day, no imputation will be performed.
Time from first dose of study intervention to first resolution of Key RSV signs/symptoms based on ObsRO after free of supplementation for at least 24 hours (hours)	Time (in hours) from first dose of study intervention until the first time of resolution of key RSV signs/symptoms based on ObsRO (please see Section 6.12) with no supplemental oxygen nor supplemental feeding hydration for at least 24h. Key RSV signs/symptoms from the ObsRO occurs when all signs/symptoms are "resolved" for approximately 24h. In order to define the approximately 24h, all ObsRO assessments will be considered and not only the ones assigned to an analysis visit. The approximate 24h resolution of the Key RSV signs/symptoms is defined with the following considerations: • **Three consecutive recordings** indicating resolution are required, **if the first** (of these 3 consecutive) recording is **before** the second analysis timepoint of the BID schedule at **Day 14**. These 3 consecutive recordings should have been done over 4 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed. • **Two consecutive recordings** indicating resolution are required, **if the first** (of these 2 consecutive) recording is **at or after** the second analysis timepoint of the BID schedule at **Day 14**. These 2 consecutive recordings

Table 6: Key Secondary Endpoints

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>should have been done over 3 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed.

Please see Section 6.10 for guidance on how to handle missing data for episodes of supplementation (oxygen and feeding /hydration).

In case of Key RSV signs/symptoms resolution after free of supplementation for at least 24h not reached, data will be censored.

<u>Censoring will be done as follows:</u>

<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>For participants with missing information prior to the event due to:
• completion
• withdrawal/early discontinuation of the study
• lost to follow up (LTFU)</td><td>Date & time of the completion, withdrawal/discontinuation of the study or LTFU accordingly.</td></tr>
<tr><td>Last record(s) indicate resolution of RSV symptoms but insufficient recordings to meet the 24h free of supplementation</td><td>At 504h from first dose of study intervention</td></tr>
<tr><td>Last record does not indicate resolution of RSV symptoms</td><td>At 504h from first dose of study intervention</td></tr>
<tr><td>Death (without previous resolution supplementation free)</td><td>At 504h from first dose of study intervention</td></tr>
</table>

$$Time\ (hours) = \frac{(Date\ \&time\ of\ event\ \ or\ censor\ ) - (Date\ \&\ time\ of\ first\ dose)}{3600}$$

$$Time\ (days) = \frac{(Date\ \&time\ of\ event\ \ or\ censor\ ) - (Date\ \&\ time\ of\ first\ dose)}{86400}$$

Time (in hours and in days) will be provided rounded to one decimal.</td></tr>
<tr><td>RSV-related complication</td><td>Any participant who experienced at least one treatment emergent adverse event (TEAE) included in the list of complications below will receive code 1 (“with complications”), participants who did not experience any of the specified TEAE will receive code 0 (“without complications”).

• 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.</td></tr>
</table>

Table 6: Key Secondary Endpoints

Measurement	Formula
	• **Acid-base or electrolyte complications**: 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 (Ca2+ <7.7 mg/dL or equivalent to Grade 2 in children ≤3 months of age), hypercalcemia (Ca2+ >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).

5.4.1.2. Analysis Methods

Clinically Resolved

A summary of the proportions of participants clinically resolved from baseline to Day 8 will be provided by intervention group.

Graphical displays and tabulations will be provided showing the proportion of participants clinically resolved by study day.

Time to resolution of Key RSV signs/symptoms (based on ObsRO) after free of supplementation for at least 24h

This time to event variable will be analyzed using Kaplan-Meier analysis. The 95% 2-sided confidence intervals will be presented.

The data will be presented graphically using the Kaplan-Meier estimate of the survival function by intervention group.

RSV-related complications

RSV-related complications will be summarized by intervention group. All details will be part of the AE listing.

5.4.2. Supportive Secondary Endpoint(s)

5.4.2.1. Definitions

The ObsRO version 9.0 cough information is collected according to questions 7a and 7b as follows:

- Question 7a: *"Did the child cough?"*
- Question 7b: *"Did coughing cause any of these problems for the child?"*

If no coughing reported in question 7a, the subsequent question 7b is not needed.

Due to an error in the instructions and subsequent eCOA device programming for question 7a, if a caregiver reported to coughing in response to question 7a, both question 7b and 8 were skipped. Question 8 collects feeding problems.

As a consequence, the changes on the planned analyses are as follows for ObsRO and ClinRO:

- feeding problems information will be available at database level but no summaries will be provided.
- only the Key RSV signs/symptom summary parameter will be derived and available in the summaries.

Due to an error in the eCOA device set up, the role of the different caregivers and clinicians rating a participant was not collected therefore, this information cannot be summarized.

5.4.2.1.1. Based on Parent/Caregivers PRESORS (ObsRO)

The parent/caregiver PRESORS (ObsRO) (please see protocol Section 10.11) is composed of 2 groups of questions:

ObsRO Section	Question(s) #	Purpose
Signs/Symptoms	1-9	Information used to monitor specific signs/symptoms of RSV disease based on observations by the child's caregiver.
General Health Questions	10-14	Caregiver's general impression of the child's RSV disease severity, change in RSV disease severity since entering the study, overall health status and return to usual health.

Table 7: Parameters based on ObsRO

Measurement	Formula
ObsRO Signs/Symptoms	
ObsRO signs/symptoms scores	Score per concept according to the score system provided in Section 6.12. The higher the score is, the worse/higher severity of the symptom/sign. Signs/Symptoms (ObsRO): breathing problems, retractions, tachypnea, breathing sounds, cough, tachycardia, nasal secretions, sleep disturbance, crying, illness behavior, feeding problems and dehydration. For days where ObsRO BID schedule, the worst score within the study day will be used for any analysis of the scores.
ObsRO signs/symptoms resolution	For each ObsRO sign/symptom, resolution will be derived based on the worst status within the study day (resolved/not resolved) of each sign/symptom (please see Section 6.12). For each sign/symptom: • RESOLVED → if all the assessments within the study day are considered resolved. • NOT RESOLVED → if at least one of the assessments within the study day is not resolved. • Missing → if no ObsRO assessment within the study day. The following categories will be assigned: Resolved (1); Not resolved (0) and Missing (2).
ObsRO Daily summary parameter score	The ObsRO Key RSV signs/symptoms summary parameter daily summary score will be calculated according to worst sign/symptom score within the study day. For the list of signs/symptoms to be considered for the summary parameter please see Section 6.12. **Average of the worst**: daily summary score will be the average of the worst score reached per sign/symptom by study day (see Table 3).
ObsRO Daily summary parameter resolution	For the ObsRO summary parameter, resolution will be derived based on the worst status within the study day (resolved/not resolved) of each sign/symptom (please see Section 6.12). For the summary parameter: • RESOLVED → if all signs/symptoms involved in the summary parameter are resolved within the study day. • NOT RESOLVED → if at least one of signs/symptoms is not resolved. • Missing → if no ObsRO assessment within the study day. The following categories will be assigned: Resolved (1); Not resolved (0) and Missing (2).

Table 7: Parameters based on ObsRO

Measurement	Formula
ObsRO General Health Questions (ObsRO GHQ)	
Status of RSV symptoms at each time point (categorical)	Each assessment of ***question 10*** '*How would you rate the child's RSV symptoms now?*' will be assigned to one of the 6 categories below: □ Recovered, no longer ill □ Very mild □ Mild □ Moderate □ Severe □ Very severe
Status of improvement of RSV symptoms at each time point (categorical)	Each assessment of ***question 11*** '*Would you say the child's RSV has improved, is about the same or is worse than when the child entered the study?'* will be assigned to one of the 5 categories below: □ Very much improved □ Much improved □ A little improved □ About the same □ A little worse □ Much worse □ Very much worse
Status of health at each time point (categorical)	Each assessment ***question 12*** '*Overall, how is the child's health now?'* will be assigned to one of the 6 categories below: □ Excellent □ Very good □ Good □ Fair □ Poor □ Very poor
Status of return to pre-RSV disease health at each time point (binary)	Each assessment of ***question 13*** *'Has the child's health returned to normal (how it was before RSV)?'* will be assigned to one of the 2 categories below: □ No, child is still ill □ Yes, child is back to normal
ObsRO General	
Missing ObsRO assessments [binary]	Missing ObsRO assessments per day, from baseline to Day 21, will be identified per analysis visit window based on the data handling rules described in Section 5.1.4, where: • Expected → number of participants for which assessment(s) per day is expected based on the BID vs QD assessment schedule per protocol. • Completed → number of participants with completed (non-missing) assessments per day and still ongoing in the study at the timepoint of interest. Noting that during the BID assessment schedule, if at least one assessment is available for that day, it is regarded as sufficient, and participant is considered to have a completed assessment.

Table 7: Parameters based on ObsRO

Measurement	Formula
	• Total missing → number of participants with at least one missing assessment per day from baseline to Day 21.

5.4.2.1.2. Based on Clinician PRESORS (ClinRO)

The Clinician PRESORS (ClinRO) (please see protocol Section 10.13 Appendix 13) of 3 groups of questions:

ClinRO Section	Question(s) #	Purpose
Signs/Symptoms	1-12	Information used to monitor specific signs/symptoms of RSV disease based on observations by the clinician.
General Health Questions*	13-15	Clinician's general impression of the child's RSV disease severity, change in RSV disease severity, and overall health status.
Additional Question		To check if participant stopped breathing at any point in the past 12 hours.

*Question 15 Clinician's Global Rating of Change (CGRC) to be completed only at Day 8 and Day 21(or last follow up visit if participant is early treatment discontinuation).

Table 8: Parameters based on ClinRO

Measurement	Formula
ClinRO Signs/Symptoms	
ClinRO signs/symptoms scores	Score per concept according to the score system provided in Section 6.13. The higher the score is, the worse/higher severity of the symptom/sign. Signs/Symptoms (ClinRO): breathing problems, retractions, tachycardia, tachypnea, wheezing, cough, nasal secretions, activity level, sleep disturbance, feeding problems, and dehydration. ClinRO BID schedule will be followed while hospitalized. For those BID days, the worst score within the study day will be used for any analysis of the scores.
ClinRO signs/symptoms resolution	For each ClinRO sign/symptom, resolution will be derived based on the worst status within the study day (resolved/not resolved) of each sign/symptom (please see Section 6.13). Same instructions/definitions as for ObsRO signs/symptom resolution apply for ClinRO ones (please see Section 5.4.2.1.1, Table 7). Please notice that for ClinRO, the category "Not Available" is considered instead of "Missing". This category includes truly missing or not expected since once participant is discharged, limited on-site visits will be performed.

Table 8: Parameters based on ClinRO

Measurement	Formula
ClinRO Daily summary parameter score	The ClinRO Key RSV signs/symptoms summary parameter daily summary score will be calculated according to worst sign/symptom score within the study day. For the list of signs/symptoms to be considered for the summary parameter please see Section 6.13. **Average of the worst**: daily summary score will be the average of the worst score reached per sign/symptom by study day (see Table 3).
ClinRO Daily summary parameter resolution	For the ClinRO summary parameter, resolution will be derived based on the worst status within the study day (resolved/not resolved) of each sign/symptom (please see Section 6.13). Same instructions/definitions as for ObsRO summary parameter resolution apply for ClinRO one (please see Table 7). Please notice that for ClinRO, the category "Not Available" is considered instead of "Missing". This category includes truly missing or not expected since once participant is discharged, limited on-site visits will be performed.
ClinRO General Health Questions (ClinRO GHQ)	
Status of overall condition at each time point (categorical)	Each assessment of ***question 13*** '*Do you have any concerns relating to the subject's overall condition'* will be assigned to one of the 3 categories below: □ No concerns (condition is stable or improving) □ Some concerns (may become unstable/requires close observation) □ Extremely concerned (unstable, requires immediate medical review)
Status of health at each time point (categorical)	Each assessment of ***question 14*** '*Overall, how would you rate the subject's current health status*' will be assigned to one of the 4 categories below: □ Excellent □ Good □ Fair □ Poor
Health compared to the baseline assessment (categorical)	Clinician's global rating of change (CGRC) ***question 15*** *"With respect to the child's RSV infection, how would you describe the child's health now compared to the baseline assessment?"* only to be answered at Day 8 and at Day 21. Ordinal scale from -3 to 3 where -3 indicates 'very much worse', 0 indicates 'unchanged', and 3 indicates 'very much improved'.
ClinRO General	
Missing ClinRO PRESORS [binary]	Missing ClinRO assessments per day, from baseline to Day 21, will be identified per analysis visit window based on the data handling rules described in Section 5.1.4, where: • Expected → number of participants for which assessment(s) per day is expected based on the hospitalized vs outpatient status and for those participants still ongoing in the study at the timepoint of interest. • Completed → number of participants with completed (non-missing) assessments per day and still ongoing in the study at the timepoint of interest

Table 8: Parameters based on ClinRO

Measurement	Formula
	and taking into account participant' status (hospitalized vs outpatient). Noting that during the BID assessment schedule, if at least one assessment is available for that day, it is regarded as sufficient, and participant is considered to have a completed assessment. • Total missing → number of participants with at least one missing assessment per day from baseline to Day 21.

5.4.2.1.3. Other Clinical Course Endpoints

Table 9: Additional Clinical Course Parameters

Measurement	Formula
Study Hospitalization (hours) [Duration]	The time from first dose of study intervention to first hospital discharge in hours. Discharge data and time information as available in Hospitalization (Inpatient) form. Time (in hours and in days) will be provided rounded to one decimal.
Re-hospitalization	If after being discharged from the hospital, participant is re-hospitalized (ward or ICU). Categories will be Yes (1) or No (0). Only derive this parameter for participants that are re-hospitalized after first discharge.
Actual intensive care unit (ICU) stay	In the Hospitalization (Inpatient) form, level of hospital care is equal to Intensive Care Unit (ICU) Categories will be Yes (1) or No (0). Only derive this parameter for participants that were not in the ICU before first dose of study intervention and experience at least one ICU stay during the study.
Duration of intensive care unit (ICU) stay (hours) [Duration]	The total number of hours of ICU episodes that a participant experienced from the first dose of study intervention until study termination. $Time\ (hours) = \sum \frac{(End\ date\ \&time\ ) - (Start\ date\ \&time)}{3600}$ If the initial start time is prior to the first dose of study drug, the duration prior to the first dose of study drug will be deducted from the overall duration. Please see Section 6.10 Missing start/end (Medical need of) ICU.

Table 9: Additional Clinical Course Parameters

Measurement	Formula
Use of oxygen supplementation	In the Oxygen Supplementation form, if any type of oxygen supplementation indicated as given. Categories will be Yes (1) or No (0). Only derive this parameter for participants that didn't receive oxygen supplementation before first dose of study intervention (no score will be assigned otherwise).
Duration of oxygen supplementation hours) [Duration]	The total number of hours of oxygen supplementation episodes that a participant experienced from the first dose of study intervention until study termination. $$Time\ (hours) = \sum \frac{(End\ date\ \&time\ ) - (Start\ date\ \&time)}{3600}$$ If the initial start time is prior to the first dose of study intervention, the duration prior to the first dose of study intervention will be deducted from the overall duration. Please see Section 6.10 Missing start/end of supplemental oxygen.
Use of non-invasive non-mechanical ventilation support	In the Oxygen Supplementation form, type of oxygen supplementation is "Non-Invasive Non-Mechanical ventilation". Categories will be Yes (1) or No (0). Only derive this parameter for participants that didn't receive oxygen supplementation before first dose of study intervention (no score will be assigned otherwise).
Use of non-invasive mechanical ventilation support	In the Oxygen Supplementation form, type of oxygen supplementation is "Non-Invasive Mechanical Ventilation" Categories will be Yes (1) or No (0). Only derive this parameter for participants that didn't receive non-invasive mechanical ventilation support or invasive mechanical ventilation support before first dose of study drug (no score will be assigned otherwise).
Use of invasive mechanical ventilation support	In the Oxygen Supplementation form, type of oxygen supplementation is "Invasive Mechanical Ventilation" Categories will be Yes (1) or No (0). Only derive this parameter for participants that didn't receive invasive mechanical ventilation support before first dose of study drug (no score will be assigned otherwise).
Use of supplemental feeding/hydration	In the Supplemental Feeding/Hydration form, "*Did the subject require supplemental (other than by mouth, i.e via nasogastric tube) feeding/hydration?*"

Table 9: Additional Clinical Course Parameters

Measurement	Formula
	Categories will be Yes (1) or No (0). Only derive this parameter for participants that didn't receive supplemental feeding/hydration before first dose of study drug (no score will be assigned otherwise).
Duration of supplemental feeding/hydration (hours) [Duration]	The total number of hours of supplemental feeding episodes that a participant experienced from the first dose of study intervention until study termination. $$Time\ (hours) = \sum \frac{(End\ date\ \&time\ ) - (Start\ date\ \&time)}{3600}$$ If the initial start time is prior to the first dose of study intervention, the duration prior to the first dose of study intervention will be deducted from the overall duration. Please see Section 6.10 Missing start/end of supplemental feeding/hydration. Only derive this parameter for participants that were not in supplemental feeding/hydration before first dose of study intervention and experienced at least one episode of medical need of supplemental feeding/hydration (as per protocol definition) during the study.

5.4.2.1.4. Medical Resource Utilization

Medical Resource Utilization will be assessed by the number and duration of medical care encounters for RSV infection or complications associated with RSV per investigator assessment.

Information will be provided as:

- Number of medical encounters and reason (AE, Other)
- Type of medical encounter such as medical practitioner office, emergency room, intensive care unit, home care, among others
- Type of practitioner
- Frequency of visits

5.4.2.1.5. RSV RNA Viral Load (qRT-PCR)

Due to early termination of the study, VL area under the curve (AUC) from Day 1 through Day 3,5 and 8 will not be determined.

Table 10: Viral Load Parameters

Measurement	Formula
Log10 viral load actual values	Log10 of the actual values as measured with qRT-PCR in nasal swab samples collected at the clinic visits and at home
Log_{10} viral load change from baseline	Change = log_{10} viral load actual value – log_{10} baseline value
Viral load status at each time point (categorical)	Each RSV viral load measurement will be assigned to one of the 3 categories below: • Undetectable (<LLOQ TND) • Detectable (<LLOQ TD) • Quantifiable (>= LLOQ)
Viral load status at each time point (binary)	Each RSV viral load measurement will be assigned to one of the 2 categories to identify if it is detectable. • Detectable or quantifiable = Yes (1) • Undetectable = No (0)

5.4.2.2. Analysis Methods

5.4.2.2.1. Based on ObsRO and ClinRO

Signs/symptoms and summary parameters

Frequency summaries over time considering status "resolved/not resolved" will be provided for each sign/symptom (except for feeding problems) and the summary parameter Key RSV signs/symptoms by intervention group. Bar plots will be provided.

ObsRO/ClinRO General Health Questions (GHQ)

Information will be available at database level, but no summaries will be provided.

Missing Data: ObsRO/ClinRO PRESORS

Summary of the number (n) and percentage (%) of participants with, at least one completed assessment by analysis visit window (baseline to Day 21), and still ongoing in the study at the timepoint of interest, will be presented overall by intervention group.

Total number of participants with completed assessments from baseline to Day 21 will be evaluated relative to the total number of participants with expected assessments taking into account the protocol-required assessment schedule.

Actual number of participants with assessments missing per analysis visit window, taking into account the protocol-required assessment schedule and participant status (hospitalized vs outpatient) at the timepoint of interest, will also be presented.

Reason of missing ObsRO and/or ClinRO assessments will be available at database level, but no summaries will be provided.

5.4.2.2.2. Other Clinical Course Endpoints

Duration of Hospitalization, ICU stay, supplemental feeding/hydration and of oxygen supplementation

Descriptive summaries for each duration will be provided by intervention group for participants with at least one episode.

For the supplementation, summaries will include the different types of each supplementation received (eg, for supplemental oxygen: requirement for no-invasive non-mechanical ventilation support, non-invasive mechanical ventilation support, or invasive mechanical ventilation support).

All information will be listed including any case of re-hospitalization.

5.4.2.2.3. Medical Encounters

Information on medical encounters (frequency of visits, type of practitioner) will be listed only.

5.4.2.2.4. RSV RNA Viral Load (qRT-PCR)

Descriptive statistics for viral load including the number of participants, mean, standard deviation (SD), standard error (SE), 95% confidence interval, median, range and interquartile range by visit and intervention group will be provided.

Mean ± SE graphs over time for the $\log_{10}$ viral load actual values and changes from baseline will be generated by visit and intervention group.

Proportion of participants with undetectable RSV viral load

The proportion of participants within the RSV RNA viral load categories (quantifiable, detectable and undetectable) will be shown in a frequency tabulation, as well as graphically, by intervention group and visit. Participants with missing data on that analysis visit will not be counted in the denominator for the proportion.

In case of co-infection with both RSV A and B, the worst category will be used for the analysis. As higher viral loads denote worse degree of infection, the ordering will be from worst to better namely: quantifiable – detectable – undetectable.

5.5. Exploratory Endpoint(s) Analysis

5.5.1. Definitions

5.5.1.1. Impact on Parents and Family

For the Parent/Caregiver General Impact Questions please refer to question 1-4 in protocol Section 10.12, Appendix 12.

The purpose of these questions is to collect information on how the child's illness is affecting caregivers' life and the lives of other people who live with the child. These are once daily optional questions for the caregivers to complete at the end of each day up to Day 21.

Table 11: Impact on Parents and Family Parameters

Measurement	Formula
ObsRO General Impact Questions (ObsRO GIQ)	
Extent of the parent's/caregiver's worry about the child's health	Based on ***question 1*** *"How are you feeling about your child's health now?"* □ I am not worried about my child □ I am slightly worried about my child □ I am moderately worried about my child □ I am severely worried about my child □ I am extremely worried about my child Extent of worry is defined as the number of days from first dose of study intervention to caregiver reporting for the first time *"I am not worried about my child".*
Time missed from usual activities by the parent/caregiver	Based on ***question 3*** *"How many hours were you unable to do things you usually do such as go to work, run errands, keep appointments, or take care of family members because my child was ill?"* Time missed from usual activities will be provided as: • Number of days where missing hours were reported • Total number of hours reported
Time missed from work by anyone in child's household due to the child's illness	Based on ***question 4*** *"What is the total number of hours missed from work for all the employed people who live with the child?"* Time will be provided as: • Number of days where missing hours were reported • Total number of hours reported

5.5.2. Analysis Methods

Information will only be available at database level. No outputs are planned for the CSR.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, SD, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE or any worsening of any 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. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as

partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs by toxicity grade
- AEs by relationship to study intervention
- SAEs by relationship to study intervention
- AEs with grade 3 or 4
- AEs leading to discontinuation of study intervention
- AEs leading to termination of study participation

In addition to the summary tables, a listing for all AEs will be provided.

Incidence of other treatment-emergent adverse events of special interest will be summarized. See Section 6.8 for list of adverse events in each category.

If any death, a listing of participants who died will be provided.

5.6.2. Additional Safety Assessments

5.6.2.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics displays will be presented for clinical chemistry, hematology and urinalysis laboratory tests at scheduled time points.

Change from baseline to scheduled time points will be summarized for chemistry and hematology tests and displayed by intervention group.

Toxicity grades will be determined according to the Division of Microbiology and Infectious Diseases (DMID) pediatric toxicity tables and the Division of AIDS (DAIDS) AE grading for Total Bilirubin (see protocol Section 10.5 Appendix 5 and Section 10.6 Appendix 6, respectively) by the central laboratory and will be attributed to the baseline and postbaseline values.

It was noted that in the DMID table (see protocol Section 10.5 Appendix 5) for children less than or equal to 3 months of age, the calcium toxicity ranges (Hypocalcemia, Hypercalcemia) provided in mEq/L correspond to the values in mg/dL instead. Due to early termination of the study, no protocol amendment was completed for this issue.

The adjusted ranges for calcium toxicity grading considered by the central laboratory for the identified age groups are as follows:

DMID table: Adjusted calcium toxicity grading (selected values for children younger than or aged 3 months)

	Grade1	Grade 2	Grade 3	Grade 4
Hypocalcemia				
< 7 days old	6.5 – 6.9 mg/dL	6.0 – 6.4 mg/dL	5.5 – 5.9 mg/dL	< 5.5 mg/dL
7 – 60 days old	7.6 – 8.0 mg/dL	7.0 – 7.5 mg/dL	6.0 – 6.9 mg/dL	< 6.0 mg/dL
61 – 90 days old	7.8 – 8.4 mg/dL	7.0 – 7.7 mg/dL	6.0 – 6.9 mg/dL	< 6.0 mg/dL
Hypercalcemia				
< 7 days old	12.0 – 12.4 mg/dL	12.5 – 12.9 mg/dL	13.0 – 13.5 mg/dL	> 13.5 mg/dL
7 – 60 days old	10.5 – 11.2 mg/dL	11.3 – 11.9 mg/dL	12.0 – 13.0 mg/dL	> 13.0 mg/dL
61 – 90 days old	10.5 – 11.2 mg/dL	11.3 – 11.9 mg/dL	12.0 – 13.0 mg/dL	> 13.0 mg/dL

In case no toxicity grades are defined for a test, the abnormalities (below/above normal ranges) will be used.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For toxicity grades, treatment emergent (TE) will be concluded if the postbaseline value is worse than the baseline value.
- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Number and percentage of participants with TE clinical laboratory tests that meet toxicity grades or criteria for abnormality values will be presented by intervention group over time.

Mean ± SE graphs over time for the actual values and changes from reference will be generated for clinical chemistry tests (except for blood urea nitrogen, creatinine, uric acid, and chloride) by intervention group.

5.6.2.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, respiratory rate (RR), weight, pulse, blood pressure and oxygen saturation (SpO_2) will be summarized at each assessment time point. Change from baseline will be summarized by intervention group.

Descriptive statistics (mean, SD, median, minimum and maximum) will be presented.

Abnormality criteria (based on criteria defined below in Table 12) will be applied to baseline and postbaseline values. Abnormality codes for body temperature are defined, as indicated in Table 13.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Table 12: Vital Signs Abnormalities – Abnormally Los/Normal/Abnormally High

Parameter (unit)	Abnormality	Age class				
		0 – 3 months	3 – 12 months	1 - 2-years	2- <3 years	3-6 years
DBP (mmHg)	abnormally low	<35	<40	<40	<40	<45
	abnormally high	>65	>85	>90	>70	>80
SBP (mmHg)	abnormally low	<60	<60	<75	<80	<80
	abnormally high	>110	>110	>120	>110	>110
Pulse/ HR (bpm)	abnormally low	<80	<70	<60	<90	<80
	abnormally high	>180	>150	>140	>130	>120
RR	abnormally low	<25	<20	<18	<20	<17
	abnormally high	>70	>60	>50	>35	>30
SpO_2 (%)	abnormally low	<92	<92	<92	<92	<92

Table 13: Abnormalities for Body Temperature

Abnormality Code	Temperature (°C)				
	Tympanic	Forehead	Oral	Rectal	Axillary
Abnormalities on actual values					
Normal	≤ 37.8	≤ 38.0	≤ 38.0	≤ 37.2	≤ 38.0
Abnormally high	> 37.8	>38.0	>38.0	>37.2	>38.0

Only measurements taken while participant was calm, not crying and in supine position for temperature, pulse, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and RR and at room air for SpO_2, will be considered in the analyses.

Number and percentage of participants with TE abnormalities will be presented by intervention group over time.

For RR, pulse/heart rate and body temperature, the maximum value will be considered as the worst grade/value while for SpO_2, the lowest value will be considered the worst one.

Mean ± SE graphs over time for the actual values and changes from reference will be generated and presented by intervention group and by age groups as assigned at screening.

5.6.2.3. Electrocardiogram

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB), Fridericia's formula (QTcF). QTcB and QTcF values will be used as reported by central ECG lab, they will not be recalculated.

Descriptive statistics (mean, SD, median and range) of ECG parameters and change from baseline will be summarized at each scheduled time point by intervention group.

Abnormality criteria (based on criteria defined below in Table 14) will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

The number and percentage of participants with TE ECG abnormalities will be presented by intervention group over time.

Table 14: ECG Abnormalities

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	0 - 2 years	NA	>150
	>2 - 5 years	NA	>160
QRS (msec)	0 - 2 years	NA	>89
	>2 - 5 years	NA	>95
QT (msec)	0 - 5 years	NA	>500
RR (msec)	0 - 3 months	<333	>750
	3 - 12 months	<400	>860
	1 - 2 years	<430	>1000
	2 - <18 years	<600	>1200
Abnormalities on the changes from baseline (ΔQTc)			
QT corrected	**Abnormality Code**		**Criteria**
	Borderline QTc change		30 ms < ΔQTc <= 60 ms
	Abnormally high QTc change		ΔQTc > 60 ms
Abnormalities on actual QTcF values			
QT corrected Formula	Abnormally high QTc value		450 ms < QTcF ≤ 480 ms 480 ms < QTcF ≤ 500 ms >500 ms

A tabulation of the worst QT/QTc change versus baseline by intervention group over time will be presented.

Mean ± SE graphs over time for the actual values and changes from reference will be generated and presented by intervention group and by age group as assigned at screening.

5.7. Other Analyses

5.7.1. Acceptability and Palatability of the rilematovir formulation

Table 15: Acceptability and Palatability endpoints

Measurement	Formula
Acceptability and palatability (categorical)	Assessment of 'In general, how did the child react when he/she was given the medicine? (note all that apply)' □ Child took medicine easily □ 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) This is only captured once during visit Day 8
Acceptability and palatability (binary)	Assessment of 'In general, how did the child react when he/she was given the medicine? (note all that apply)' Category will be 'Acceptable' (1) if answered: □ Child took medicine easily Category will be 'Partly or Not Acceptable' (0) in case any of the following was answered: □ 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) This is only captured once during visit Day 8

The proportion of participants within the categories will be shown in a frequency tabulation, as well as graphically, per intervention group.

5.7.2. Pharmacokinetics

PK data may be listed.

5.7.3. Virology

5.7.3.1. Definitions

Viral Strain Typing

The RSV subtype is determined at baseline using the RSV-A/B RT-qPCR assay performed in the central lab.

Viral Sequencing

Viral resistance will be evaluated by next-generation sequencing (NGS) of the RSV Fusion (F) gene using a read frequency cut-off of 3%.

Baseline samples from all participants will be sequenced to identify pre-existing genetic variations in the RSV F gene. Post-baseline sequencing will be performed on the last evaluable on-treatment sample and/or during follow-up for all participants (if viral load is high enough) to identify emerging amino acid substitutions in the RSV F gene. Additional post-baseline sequencing can be performed on request of the sponsor virologist.

Genetic variations

Genetic variations are defined as changes (on amino acid or nucleotide level) in the participant's viral sequence compared to a reference sequence. Genetic variations can include substitutions, insertions and deletions. The reference sequences used will be RSV-A Long strain (GenBank Accession number AY911262) for RSV-A samples and RSV-B strain 9320 (GenBank Accession number AY353550) for RSV-B samples. Genetic variations will be reported on amino acid level.

- **Baseline genetic variation**: amino acid difference from the RSV-A or RSV-B reference strain detected at baseline with an NGS read frequency ≥15%.
- **Emerging genetic variation:** a genetic variation (amino acid substitution, insertion or deletion) that is absent, ie. with a NGS read frequency <3%, at baseline but detected with a NGS read frequency ≥15% at a later post-baseline time point.
- **Enriched genetic variation**: a genetic variation (amino acid substitution, insertion or deletion) detected at baseline with a NGS read frequency ≥3% and <15%, and with an increase in NGS read frequency of at least 15% post-baseline.
- **Genetic variation profile**: a specific genetic variation or combination of genetic variations at one or more time points
- **RSV F protein amino acid positions of interest**:
  - Short list of 8 F protein positions of interest for JNJ-53718678, based on in vitro selection experiments with JNJ-53718678 and/or in vitro reduced susceptibility to JNJ-53718678: positions 141, 143, 394, 398, 400, 486, 488, and 489
  - Long list of 24 F protein positions of interest for the class of RSV fusion inhibitors, based on in vitro selection experiments, clinical observations, and/or in vitro reduced susceptibility to RSV fusion inhibitors, as well as residues involved in binding of JNJ-

53718678 to the RSV prefusion F protein: positions 127, 137, 138, 140, 141, 143, 144, 323, 338, 339, 392, 394, 396, 397, 398, 399, 400, 401, 474, 486, 487, 488, 489, and 517.

Analysis Time Points

Instead of the analysis phases defined in Table 2, sequencing data will follow the phases as per protocol:

Table 16: Sequencing Phases

Phase	Start Date/Time	End Date/Time
Screening	00:00 of the date of signing the informed consent form	1 minute before the first bid dose study intervention administration in the trial
Treatment	Date/time of first bid dose study intervention administration in the trial	23:59 of the last day of study intervention administration or 23:59 of the cut-off date for the IA, or 23:59 of the date of trial termination, whichever comes first
Follow-up	1 minute after the End of Intervention Phase	23:59 of the day of trial termination (date of last contact) or 23:59 of the cut-off date for the IA, whichever comes first

Virology results will be assigned to the visits at which samples for RSV F gene sequencing are collected, the below time points will be considered:

- Baseline (BL): Time point with sequencing data available closest prior to the first dose. This will be the Day 1 pre-treatment sample; however, if RSV F gene sequencing data cannot be obtained from this sample, the screening sample may be used for sequencing.
- Last Evaluable On-treatment Time Point: Last available post-baseline time point during the treatment phase with sequencing data available. In case no On-Treatment assessment is available, the first assessment during Follow-Up is selected instead.
- Any post-baseline time point in the study with sequencing data available.

5.7.3.2. Analysis Methods

Participants with baseline RSV A+B co-infection will be excluded from the summary tables.

Baseline

The prevalence of baseline genetic variations in the RSV F gene (complete RSV F gene or considering the positions of interest), ie, the number of participants with baseline genetic variations in the RSV F gene, will be tabulated in frequency outputs (n, %).

Post-baseline

Emerging and enriched genetic variations in the RSV F gene (complete RSV F gene or considering the positions of interest) will be tabulated by analysis time point in frequency outputs (n, %).

Over the study period

Amino acid changes from reference sequence at baseline and post-baseline will be listed for all participants using a NGS read frequency cut-off of 3%. For participants with emerging or enriched genetic variations, RSV RNA viral load profiles including emerging or enriched genetic variations per time point, will be generated.

5.7.4. Definition of Subgroups

Due to early termination of the study, no subgroups will be defined.

5.8. Interim Analyses

Please see details in protocol Section 9.5 Interim Analysis.

Due to early termination of the study, no interim analysis will be performed.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

Please see details in protocol Section 9.6 Independent Data Monitoring Committee and in associated IDMC charter.

Due to early termination of the study, the number of participants required for the first safety review was not reached. No further IDMC activities are foreseen nor IDMC SAP will be generated.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase
APAC	Asia Pacific, Oceania and Japan
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
bid	twice daily
CGRC	Clinician Global Rating of Change
CI	confidence interval
ClinRO	Clinician Reported Outcome
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DAIDS	Division of AIDS
DMID	Microbiology and Infectious Diseases
DBP	Diastolic blood pressure
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
EMEA	Europe, Middle East and Africa
FAS	full analysis set
FDA	Food and Drug Administration
h	hours
HR	Heart rate
IA	Interim Analysis
ICE	Intercurrent event
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IQ	interquartile
ITT-i	Intent-to-treat infected
IWRS	interactive web response system
KM	Kaplan-Meier
LATAM	Latin America and the Caribbean
LLOQ	lower limit of quantification
LOD	limit of detection
LFTU	lost to follow up
LRTI	Lower Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America (Canada and USA)
NGS	Next-generation sequencing
ObsRO	Observer Reported Outcome
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetics analysis set
QTcB	Bazett's formula QT
QTcF	Fridericia's formula QT
RR	respiratory rate
RRS	RSV Recovery Scale
SAE	serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

SC	Sponsor Committee
SD	standard deviation
SE	standard error
SMQs	standardised MedDRA queries
SoA	Schedule of Activities
SOC	Standard- of- Care
SpO_2	Oxygen saturation
TD	Target detected
TE	Treatment Emergent
TEAE	treatment-emergent adverse event
TND	Target not detected
URTI	Upper Respiratory Tract Infection
V	volume distribution
VL	Viral Load
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Please see Section 1.1.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, and overall.

Table 17 and Table 18 present a list of the demographic and baseline characteristics variables that will be summarized by intervention group and overall, for the ITT-i and SAF sets. If ITT-i identical to SAF set, summaries will be provided only for the SAF set.

Table 17: Demographics variables

VARIABLE	SUMMARY TYPE
Continuous Variables:	
Age (days, months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Weight (kg)	
Length/Height at baseline (cm)	
Head Circumference (cm)	
Categorical Variables	
Age ≥28 days and <3 months, ≥3 months and <6 months, ≥6 months and ≤5 years.)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, unknown, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not reported, Unknown)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)	
Country	
Region (Asia-Oceania (APAC), Europe and Middle East and Africa (EMEA), North America (NA), and Latin America and the Caribbean (LATAM)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 18: Baseline Characteristics

VARIABLE	SUMMARY TYPE
Continuous Variables:	
Duration RSV signs/symptoms prior to randomization (days)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Post gestational Age (weeks)	
RSV Viral Load (log_{10} copies/ml)[1]	
RSV Viral Load (log_{10} copies/ml) [1] by RSV Subtype	
Respiratory Rate (breaths/min)	
Heart Rate (beats/min)	
Oxygen saturation (%)	
Pre-RSV infection oxygen saturation (%) measured on room air	
Categorical Variables	
Baseline RSV Subtype (RSV A, RSV B, RSV A+B)	
Presence of risk factors for severe RSV disease (no, yes)[2]	
Each of the following risk factors for severe RSV disease (subcategories of the above): - prematurity at birth[3] - bronchopulmonary dysplasia - congenital heart disease	

Table 18: Baseline Characteristics

VARIABLE	SUMMARY TYPE
- Down syndrome - neuromuscular impairment - cystic fibrosis - recurrent wheezing - asthma - other congenital disease	Frequency distribution with the number and percentage of participants in each category.
Receiving Supplemental Oxygen prior to first intake of study medication (no, yes)	
Prenatal Smoking by the participant's mother (no, yes)	
Exposed to tobacco smoke in home environment (no, yes)	
History of >1 episode of wheezing without a cold (no, yes)	
History of atopic dermatitis (eczema) (no, yes)	
History of allergy (no, yes)	
If yes, type of allergy (allergic dermatitis, allergic rhinitis, allergic bronchitis, food allergy)	
History of asthma (no, yes)	
Contact with HCP before presenting (no, yes)	
If yes, type of HCP (General Practitioner, Pediatrician, Other)	
Breastfeeding (no, yes)	
Number of siblings within the household (0,1,2 or more)	
Routinely attending daycare (no, yes)	
Is the known pre-RSV SpO_2 <92%? (Yes/No)	
Pre-RSV infection oxygen saturation measured on room air	
Received palivizumab (no, yes)	
Received aerosolized ribavirin (no, yes)	
Received IV immunoglobulin (no, yes)	
Presence of other respiratory infection (no, yes)	
Presence of other respiratory viral infection (no, yes)	
Presence of other respiratory bacterial infection (no, yes)	

[1] Only Nasal Swab type samples to be considered.

[2] As per IWRS and based on eCRF data.

[3] 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. 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).

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- PD1- Entered but did not satisfy criteria
- PD2- Received a disallowed concomitant treatment
- PD3- Received wrong treatment or incorrect dose
- PD4- Developed withdrawal criteria but not withdrawn
- PD5- Other

The deviations from the protocol with major impact on the assessment of efficacy will be defined. The final set of deviations will be identified and documented prior to database lock based on the following criteria.

- PD1- Entered but did not satisfy criteria
  - PD1_IC4: Participant was enrolled, although the participant has not been diagnosed with RSV infection
  - PD1_IC5: Participant was enrolled, although the participant has no acute respiratory illness with at least 1 of the signs/symptoms listed in each of the 3 categories within 24 hours prior to start of screening and at screening
  - PD1_IC6: Participant was enrolled, although the time of onset of RSV signs/symptoms to the anticipated time of randomization was not ≤3 days
  - PD1_EX3: Participant was enrolled, although the participant is considered by the investigator to be immunocompromised
  - PD1_EX5: Participant was enrolled, although the participant has had confirmed SARS-CoV-2 infection during the four weeks prior to randomization OR participant was enrolled, although the participant has had close contact with a person with COVID-19 within 14 days prior to randomization
  - PD1_EX6: Participant was enrolled, although the participant is being treated with extracorporeal membrane oxygenation
  - PD1_EX7: Participant was enrolled, although the participant is receiving chronic (home) oxygen therapy at the time of screening
  - PD1_EX9: Participant was enrolled, although participant's mother received an investigational RSV vaccination during the pregnancy for this child and whose age is <3 months at time of screening
  - PD1_EX13: Participant was enrolled, although the participant is unable to take medications orally OR participant was enrolled, although the participant 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

- PD2- Received a disallowed concomitant treatment
- PD3- Received wrong treatment or incorrect dose
  - Participant's actual intervention not the same as planned one:
    - PD3_1: Receiving wrong medication kit
    - PD3_2: Receiving incorrect dose
  - PD3_6: Participant missed 2 or more doses
- PD4- Developed withdrawal criteria but not withdrawn
  - PD4_6: Unplanned unblinding has taken place during the study
- PD5- Other
  - PD5_2: More than 1 of every 4-consecutive scheduled ObsRO are missing between D1-D7
  - PD5_3: More than 1 of every 4-consecutive scheduled ObsRO are missing between D8-D14
  - PD5_4: More than 1 of every 3-consecutive scheduled ObsRO are missing from D15-D21
  - PD5_6: ClinRO at the day of discharge and/or next assessment after discharge is not available

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day and time (if available) of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day and time as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC class up to level 3, intervention group, intervention phase and combination of intervention and follow-up phase. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. Prior medications will be summarized by intervention group and class up to level 3.

6.6. Appendix 6 Medical History

A list of risk factors for severe RSV disease by participant will be provided. The medical history and family history records will also be listed.

6.7. Appendix 7 Intervention Compliance

Compliance will be summarized descriptively for each intervention group. The reasons for not administered doses will be listed

Intervention Compliance (%) = 100 x number of doses of study agent /total doses planned

The total planned doses are as follows:

- For participants who complete the 7 days of study intervention, a total of 14 doses will be given as per protocol
- For early study intervention discontinuation, total doses will be based on the number of days participant was in the intervention period (eg: 2 doses per day are planned by protocol so if participant is 3 days in the intervention period, total planned doses are 6).

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

Table 19: Hepatobiliary Effects

MedDRA Preferred Term (PT)	MedDRA Code
Drug-induced liver injury	10072268
Hyperbilirubinaemia	10020578
Jaundice	10023126
Ocular icterus	10058117
Yellow skin	10048245
Alanine aminotransferase increased	10001551
Aspartate aminotransferase increased	10003481
Bilirubin conjugated increased	10004685
Bilirubin urine present	10077356
Blood bilirubin increased	10005364
Blood bilirubin unconjugated increased	10005370
Gamma-glutamyltransferase increased	10017693
Blood alkaline phosphatase increased	10059570
Hypoalbuminaemia	10020942
Urobilinogen urine decreased	10070480
Urobilinogen urine increased	10070479
Allergic hepatitis	10071198
Hepatic cytolysis	10049199
Hepatitis	10019717
Hepatitis acute	10019727
Hepatitis cholestatic	10019754
Hepatitis chronic active *	10019755
Hepatitis chronic persistent *	10019759
Hepatitis fulminant	10019772
Hepatitis toxic	10019795
Immune-mediated hepatitis	10078962
Non-alcoholic steatohepatitis	10053219
Steatohepatitis	10076331

*actual represents 'acute on chronic hepatitis'.

Table 20: Cardiac Events Potentially Related to QT Prolongation[1]

MedDRA Preferred Term (PT)	MedDRA Code
Electrocardiogram QT interval abnormal	10063748
Electrocardiogram QT prolonged	10014387
Long QT syndrome	10024803
Long QT syndrome congenital	10057926
Torsade de pointes	10044066
Ventricular tachycardia	10047302
Cardiac arrest	10007515
Cardiac death	10049993
Cardiac fibrillation	10061592
Cardio-respiratory arrest	10007617
Electrocardiogram repolarisation abnormality	10052464
Electrocardiogram U wave inversion	10062314
Electrocardiogram U wave present	10057913
Electrocardiogram U-wave abnormality	10055032
Loss of consciousness	10024855
Sudden cardiac death	10049418
Sudden death	10042434
Syncope	10042772
Ventricular arrhythmia	10047281
Ventricular fibrillation	10047290
Ventricular flutter	10047294
Ventricular tachyarrhythmia	10065341

6.9. Appendix 9 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on Division of Microbiology and Infectious Diseases (DMID) pediatric toxicity tables and the Division of AIDS (DAIDS) AE grading for Total Bilirubin (see protocol Section 10.5 Appendix 5 and Section 10.6 Appendix 6, respectively).

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

6.10. Appendix 10 Missing Data

- **Missing SpO_2 (or not measured on room air) for the RRS**

	Supplemental Oxygen episode	Imputation RRS category/status
Missing SpO_2 or NOT measured-on room air	Yes	4 = Non-ICU Hospitalization, Requiring Supplemental Oxygen AND/OR Supplemental Feeding/Hydration
	No	• If **no** supplemental feeding → 3=Non-ICU Hospitalization, Not Requiring Supplemental Oxygen NOR Supplemental Feeding/Hydration • If supplemental feeding → 4= Non-ICU Hospitalization, Requiring Supplemental Oxygen AND/OR Supplemental Feeding/Hydration

- **Missing Start/End of an Oxygen Supplementation episode**

START					END				
	If first record		**If previous record**			**If no other record available**		**If a following record available**	
DATE	Impute with date of 1st dosing		impute with end date of previous record		DATE	impute with the day before**discharge* date		impute with start date of following record	
	DATE		DATE			DATE		DATE	
	Missing	Non-Missing	Missing	Non-Missing		Missing	Non-Missing	Missing	Non-Missing
TIME	impute with time of first dosing	Impute with 00:00 (Earliest in the day)	impute with end time +1 minute of previous record	Impute with 00:00 (Earliest in the day)	TIME	impute with 12h before discharge time	Impute with 23:59 (Latest in the day)	impute with start time -1 minute of following record	Impute with 23:59 (Latest in the day)

* In case of re-hospitalization, the timeframe between start date and closer discharge date to be considered.
** a) If discharge date & time available: If missing Date & time, time will be imputed with 12h before discharge time and date can be adjusted accordingly:
1- if by counting 12h back still on the same date than discharge → discharge date = end date of O2 supplementation
2- if by counting 12h back we go to the day before → discharge date -1 day = end date of O2 supplementation
b) If discharge date not available: date is imputed with end of study (or study discontinuation) date and time with 23:59

- **Missing Start/End of Supplemental Feeding/Hydration episode**

START					END				
	If first record		**If previous record**			**If no other record available**		**If a following record available**	
DATE	Impute with date of 1st dosing		impute with end date of previous record		DATE	impute with the day before**discharge* date		impute with start date of following record	
	DATE		DATE			DATE		DATE	
	Missing	Non-Missing	Missing	Non-Missing		Missing	Non-Missing	Missing	Non-Missing
TIME	impute with time of first dosing	Impute with 00:00 (Earliest in the day)	impute with end time +1 minute of previous record	Impute with 00:00 (Earliest in the day)	TIME	impute with 12h before discharge time	Impute with 23:59 (Latest in the day)	impute with start time -1 minute of following record	Impute with 23:59 (Latest in the day)

* In case of re-hospitalization, the timeframe between start date and closer discharge date to be considered.
** a) If discharge date & time available: If missing date & time, time will be imputed with 12h before discharge time and date can be adjusted accordingly:

1- if by counting 12h back still on the same date than discharge → discharge date = end date of supplemental feeding/hydration
2- if by counting 12h back we go to the day before → discharge date -1 day = end date of supplemental feeding/hydration

b) If discharge date not available: date is imputed with end of study (or study discontinuation) date and time with 23:59

- **Missing Start/End Hospitalization**

1. Imputation for actual hospitalization after confirming that discharge didn't take place
   - If actual end date missing & medical need end date missing → consider the last date of any supplementation +12h
   - If actual end date missing & medical need end date available → consider the last date of the medical need date AND any supplementation +12h
2. In case the end date is known but time is missing and supplementation ended at least the day before hospitalization end, time is imputed with 12:00.
3. In case the end date/time is completely missing and it is the last record, and the end of supplementation is also missing, date is imputed with end of study (or study discontinuation) date and time with 23:59

	START			END	
	If first record	**If previous record**		**If no other record Available-discharge***	**If a following record available**
DATE	Impute with date of 1st dosing	impute with end date of previous record	DATE	Please see above point 1,3	impute with start date of following record
TIME	impute with time of first dosing	impute with end time +1 minute of previous record	TIME	Please see above point 2,3	impute with start time -1 minute of following record

*In case of re-hospitalization, the timeframe between start date and closer discharge date to be considered.

- **Missing Start/End ICU**

START					END				
	If first record		**If previous record**			**If no other record available**		**If a following record available**	
DATE	Impute with date of 1st dosing		impute with end date of previous record		DATE	impute with the day before**discharge* date		impute with start date of following record	
	DATE		DATE			DATE		DATE	
	Missing	Non-Missing	Missing	Non-Missing		Missing	Non-Missing	Missing	Non-Missing
TIME	impute with time of first dosing	Impute with 00:00 (Earliest in the day)	impute with end time +1 minute of previous record	Impute with 00:00 (Earliest in the day)	TIME	impute with 36h before discharge time	Impute with 23:59 (Latest in the day)	impute with start time -1 minute of following record	Impute with 23:59 (Latest in the day)

* In case of re-hospitalization, the timeframe between start date and closer discharge date to be considered.
** a) If discharge date & time available: If missing Date & time, time will be imputed with 36h before discharge time and date can be adjusted accordingly:

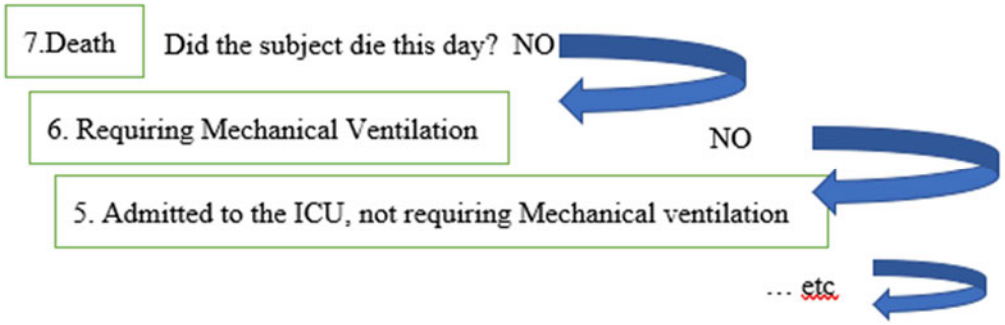
1- if by counting 36h back still on the day before discharge date → (discharge date -1 day) = end date of ICU
2- if by counting 36h back two days before discharge date → (discharge date -2 days) = end date ICU

b) If discharge date not available: date is imputed with end of study (or study discontinuation) date and time with 23:59

6.11. Appendix 11 RRS derivation

The RRS is evaluated by study day, from Day 1 to Day 8. Day 1 is defined as the day of the first dose of study intervention intake. Time of dosing is irrelevant when deriving the RRS for each study day.

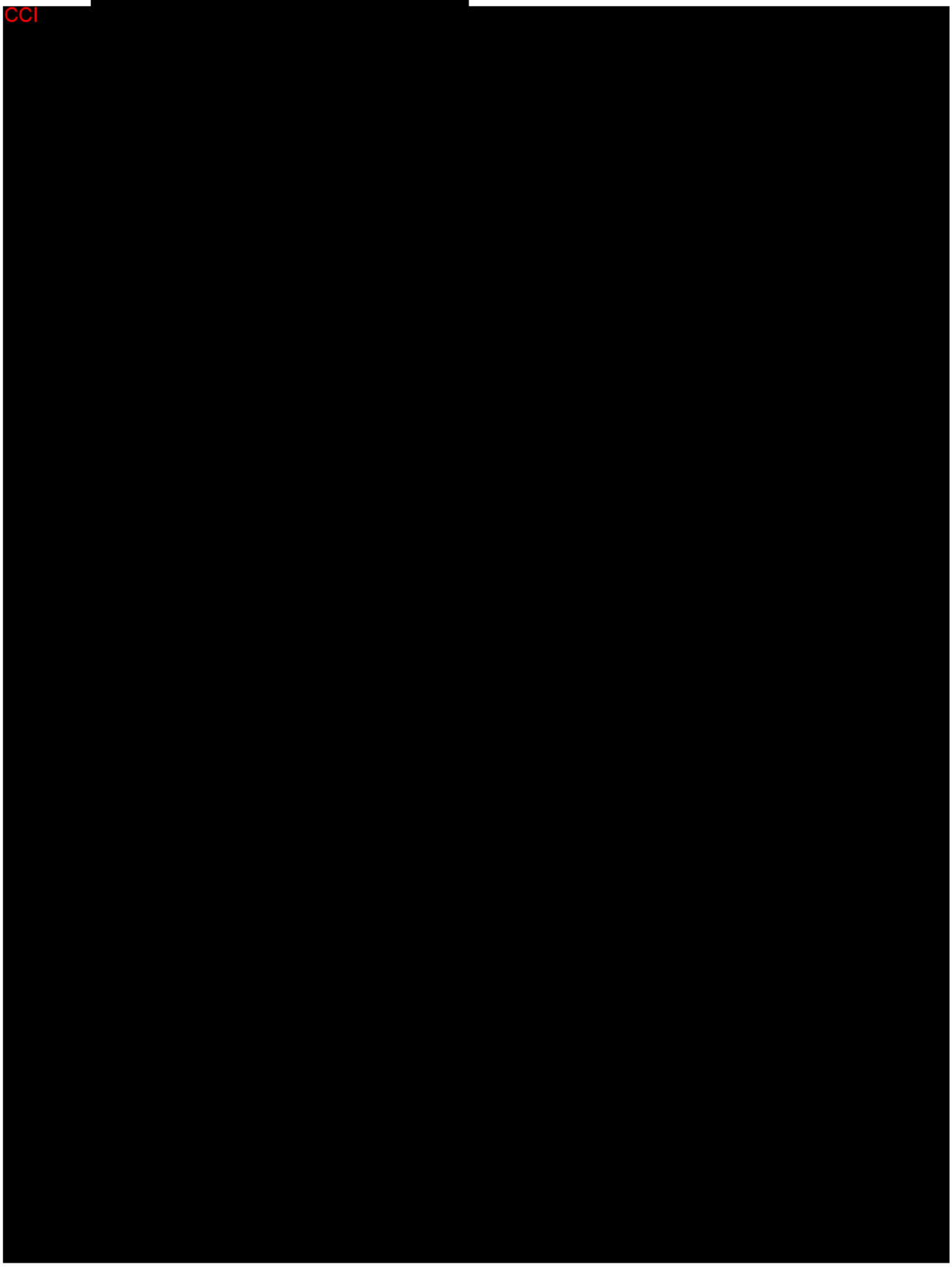
The RRS categories should be evaluated from worst category (7. Death) to the best one (1. Not hospitalized without signs/symptoms). For each study day, first would check if participant died and if not then the following category 6 will be evaluated. If participant not in that status either, next category 5 will be evaluated and so on until there is one category that participants is allocated to.



Please see Section 6.10.

6.12. Appendix 12 CCI

CCI



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6.13. Appendix 13 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

7. REFERENCES

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. ICH 12 May 2005

2. United Nations publication, Standard Country or Area Codes for Statistical Use (M49 standard), https://unstats.un.org/unsd/methodology/m49/