Janssen Research & Development

Statistical Analysis Plan

A Two-Part Study With a Birth Cohort (Observational Stage) for Early Diagnosis of Respiratory Syncytial Virus (RSV), Followed by an Optional Phase 2a, Randomized, Double-blind, Placebo-controlled Study (Interventional Stage) to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of JNJ-53718678 in Infants With Acute Respiratory Tract Infection due to RSV

JNJ-53718678RSV2006; Phase 2A

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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ABBREVIATIONS

AE	adverse event
AFT	accelerated failure time
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
CI	confidence interval
ClinRO	clinician reported outcomes
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
HR	Heart Rate
IA	interim analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ITT-i	Intent-To-Treat-infected
IQ	interquartile
IQR	interquartile range
IWRS	interactive web-based response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
ObsRO	observer reported outcomes
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
PRESORS	Pediatric RSV Electronic Symptom and Outcomes Rating System
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RAND	randomized
RR	Respiratory Rate
RSV	respiratory syncytial virus
RT	Randomized or treated
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Sponsor Committee
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	standard of care
TEAE	treatment-emergent adverse event
TD	target detected
TND	target not detected
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for study 53718678RSV2006 including efficacy and safety of the investigational compound JNJ-53718678. The SAP is to be interpreted in conjunction with the protocol.

This SAP covers the analyses for the observational stage and interventional stage of the protocol. Sections 2 to 7 describe the analyses for the interventional stage. The analyses for the observational stage are covered in Section 8. Details on the Independent Data Monitoring Committee (IDMC) analyses are provided in a separate IDMC SAP.

There will not be PK/PD modelling in this study given the small sample size. Analysis will be limited to listings and no Clinical Pharmacology Analysis Plan (CPAP) will be provided.

JNJ-53718678 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.

1.1. Trial Objectives

This study is designed to assess in the setting of a planned early interception of pediatric RSV disease, early viral and disease kinetics (observational stage) and the antiviral effects of an RSV fusion inhibitor, JNJ-53718678 (interventional stage). The objectives of the study are:

Part 1: Observational Stage

The *objectives* applied to the observational stage are to evaluate:

- the onset and evolution of clinical symptoms of pediatric RSV disease
- the relationship between viral load and clinical symptoms at early diagnosis of pediatric RSV disease

The *exploratory objectives* applied to the observational stage are to evaluate:

- the characteristics of the scores that trigger a site-visit in relation to:
  - RSV diagnosis
  - the progression of clinical symptoms
  - viral kinetics
  - participation in the interventional stage
- the correspondence between disease characteristics as assessed at the site with scores as assessed by parent(s)/caregiver(s) in the RSV mobile Application (App) and Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS)
- parent(s)/caregiver(s) baseline characteristics in relation to operational features such as:
  - enrollment in observational stage
  - RSV mobile App compliance

  - protocol adherence
  - enrollment in interventional stage
- the analysis of stool microbiome profiles (in optional samples) in relation to RSV disease

Part 2: Interventional Stage

The *primary objective* is to evaluate:

- the antiviral activity of JNJ-53718678 as measured by RSV viral load in nasal swab samples by a quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay in an early intervention setting in infants (≤4 months of age at enrollment) recruited from a birth cohort

The *secondary objectives* are to assess:

- the impact of treatment with JNJ-53718678 on the clinical course of RSV infection
- the safety and tolerability of JNJ-53718678 after repeated oral doses
- the PK of JNJ-53718678 after repeated oral doses

The *exploratory objectives* are to assess:

- the impact of baseline characteristics on antiviral activity and clinical course, including but not limited to:
  - baseline viral load
  - disease severity
  - hospitalized participants vs outpatients
  - parental history of atopy
  - randomization within 24 hours of ARI alert vs. ≥24 hours
- the relationship between the PK and antiviral activity and safety parameters after repeated dosing of JNJ-53718678
- the emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678

1.2. Trial Design

This study is designed to assess the impact of early interception and intervention on antiviral activity and the clinical course of the disease. The study consists of 2 parts: an observational stage with a birth cohort and a Phase 2a, multicenter, randomized, double-blind, placebo-controlled interventional stage.

In the observational pre-diagnostic phase, the study aims to record early signs and symptoms of potential RSV infections and is focused on bringing the infant in for assessment at a threshold score. All infants will be closely monitored for early signs and symptoms of RSV disease using a mobile RSV App on the parent/caregiver's mobile phone (pre-diagnostic phase). For those infants with scores that cross the threshold score an alert will be sent and they will be brought to the study

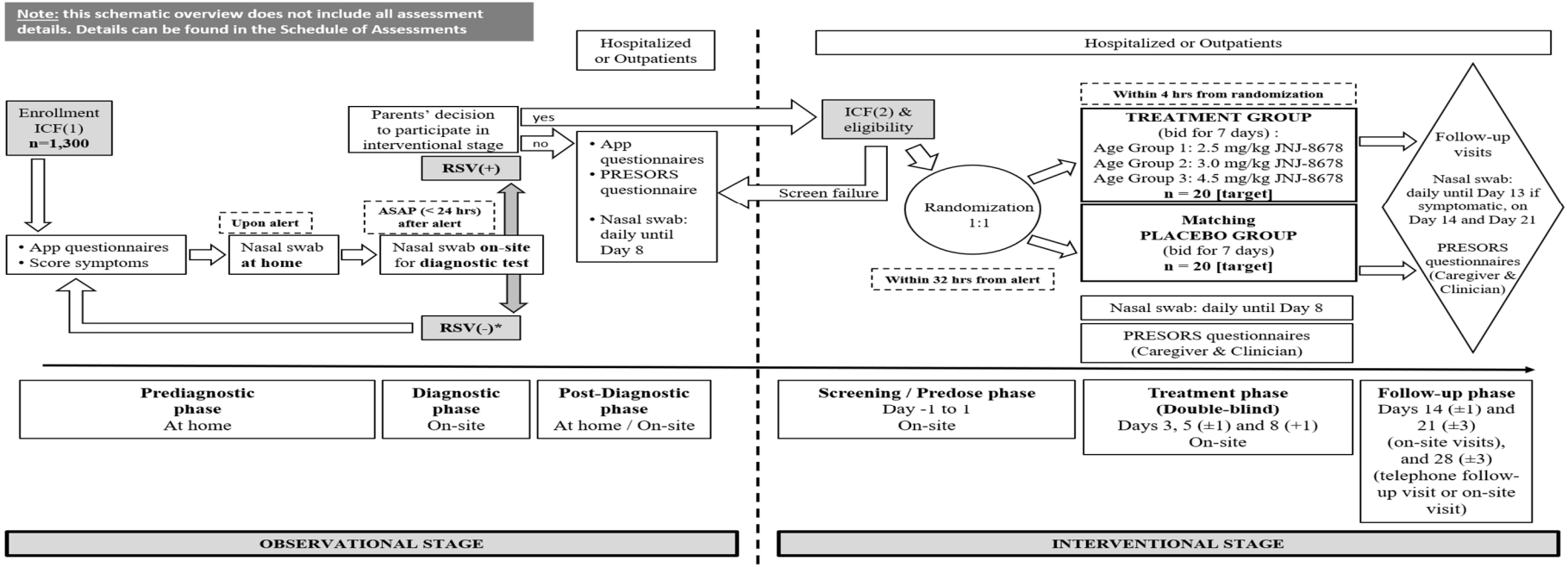
site for an early diagnostic RSV test (diagnostic phase). RSV positive (RSV [+]) participants will be enrolled in the screening phase of the interventional stage of the study after obtaining informed consent for the interventional stage at that time. RSV (+) participants whose parent(s)/caregiver(s) do not consent for enrollment in the interventional stage and participants who are screening failures in the interventional stage will enter the post-diagnostic phase of the observational stage (hospitalized or outpatients).

The interventional stage will consist of a screening phase (Day -1 to Day 1), a treatment phase (Day 1 to Day 8 [±1]), and a post-treatment follow-up phase (Day 9 to Day 28 [±3]). Participants will be randomized in a 1:1 ratio to receive either JNJ-53718678 or placebo twice daily (bid) for 7 days. A diagram of the study design is provided in Figure 1.

A target of 1,300 infants (≤4 months of age at enrollment and asymptomatic for acute respiratory infection (ARI)-like symptoms requiring medical intervention at the time of consent) is planned to be enrolled globally in the observational stage of this study. It is anticipated that approximately 40 RSV (+) infants from the observational stage of the study will be enrolled in the interventional stage. Participants should be ≥28 days old (or ≥3 months postnatal age for prematurely born infants) and at least 2.4 kg to be eligible for enrollment in the interventional stage of the study.

Study duration will be approximately 29 (±3) days after RSV (+) diagnosis for participants who enter the interventional stage, and 21 (±3) days after RSV (+) diagnosis for participants who do not enter the interventional stage. RSV negative (RSV [-]) participants will be considered to have completed the study at the end of the RSV circulation.

Figure 1: Schematic Overview of the Design of Study 53718678RSV2006



*If the participant is RSV(-) at the RSV-like acute respiratory infection (ARI) visit, the parent(s)/caregiver(s) will continue completion of the mobile App questions, alerts will be paused for 7 days.

bid=twice daily; ICF=informed consent form; PRESORS= Pediatric RSV Electronic Severity and Outcome Rating System; RSV= respiratory syncytial virus

For dosing purposes, 3 age groups are defined depending on the subject's age at the time of consent:

- Age group 1: ≥28 days and <3 months of age (28 to 91 days of age, extremes included, for IWRS purposes)
- Age group 2: ≥3 months and <6 months of age (92 to 182 days of age, extremes included, for IWRS purposes)
- Age group 3: ≥6 months (183 days of age or older, 183 included, for IWRS purposes).

Study drug will be administered on a once daily (QD) schedule (before protocol amendment 2) or a twice daily (BID) schedule (after protocol amendment 2) for 7 days. Doses are based on body weight and age group:

- JNJ-53718678 Total daily dose (n = 20 [target]):
  - Age group 1: 2.5 mg JNJ-53718678/kg bodyweight
  - Age group 2: 3 mg JNJ-53718678/kg bodyweight
  - Age group 3: 4.5 mg JNJ-53718678/kg bodyweight
- Placebo (n = 20 [target]):
  - Age groups 1, 2, and 3: matching placebo (volume of placebo suspension to match the calculated volume of the JNJ-53718678 suspension)

1.3. Statistical Hypotheses for Trial Objectives

Part 1: Observational Stage

For the observational stage, no formal hypothesis will be tested.

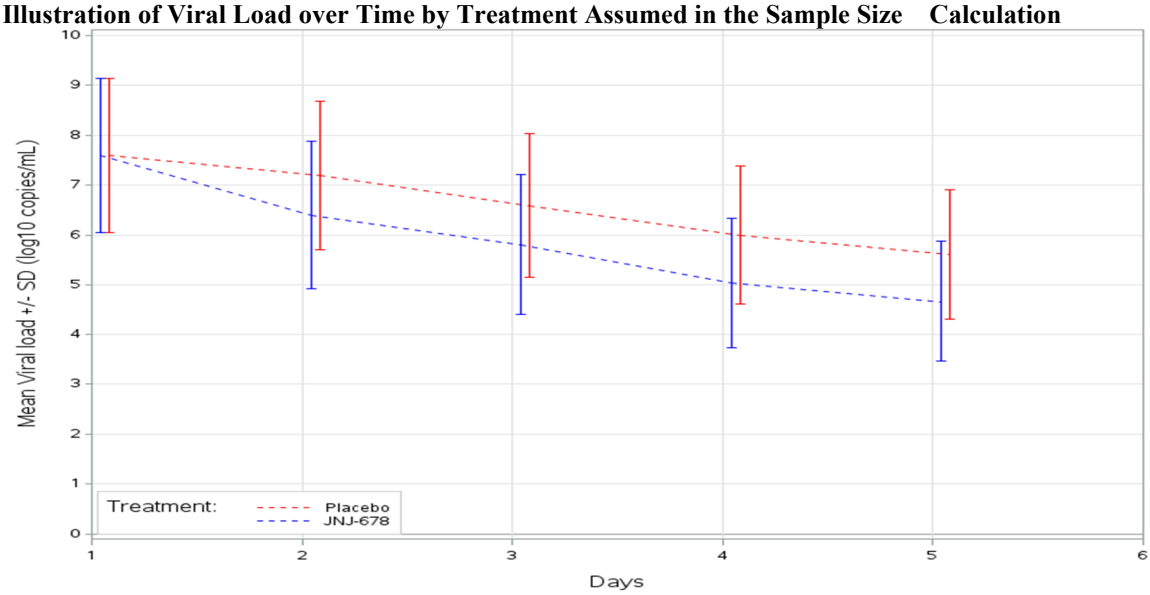
Part 2: Interventional Stage

The primary hypothesis of this study is that JNJ-53718678 has antiviral activity against RSV as assessed by a reduction in RSV viral load area under the curve (AUC) (from immediately prior to first dose of study medication [baseline] until Day 5) at the 5% level (one-sided) for JNJ-53718678 compared to placebo in participants recruited from a birth cohort.

1.4. Sample Size Justification

The sample size of the interventional stage is based on results obtained in an earlier birth cohort study (Janssen R&D, data on file) and the specified analysis method using simulated data. Based on 10,000 simulated datasets of 40 participants, with an assumed 10% drop-out rate and an effect size of early treatment of 0.75 $\log_{10}$ copies.day/mL reduction in viral load versus placebo on average (as illustrated in Figure 2), there is a power of 88% to reject the null hypothesis of no antiviral effect of JNJ-53718678 treatment using a significance level of 5% (one-sided).

Figure 2: Illustration of Viral Load over Time by Treatment Assumed in the Sample Size Calculation



The sample size of the birth cohort is based on the sample size required for the interventional stage. It is assumed based on the results of a previous observational birth cohort study (Janssen R&D, data on file) that approximately 10% of the infants participating in the birth cohort will be diagnosed as RSV (+) and will develop ARI disease signs compatible with a minimum disease severity threshold for intervention.

At the stage of the temporary hold of the interventional stage of the study on 2 March 2020, 862 infants were enrolled in the birth cohort, leading to 29 infants who were diagnosed as RSV (+) and 20 infants who participated in the interventional stage. The incidence of RSV (+) was lower than anticipated at the time of initial protocol writing, which for a large part may be explained by the relatively late in the RSV season start of recruitment for the first participating country in the study (Panama). It is assumed that when recruitment into the birth cohort is re-initiated in time for the next season, ~10% of participants will be diagnosed as RSV (+). In order to maintain the target of 40 participants in the interventional part, the maximum number of infants that may be recruited in the birth cohort is set at 1,300. With an additional 438 participants in the birth cohort, an assumption of 10% incidence of RSV (+) and a 50% rate of infants who will enter the interventional stage, the target of 40 participants in the interventional stage is expected to be reached.

As the sample size of the 2 parts are linked and assumptions have to be made on the percentages of RSV (+) and eligibility, the study may continue at the discretion of the sponsor when more than 40 participants are included in the interventional stage (with a maximum of 60) and may also be considered completed if at least 32 infants have been included the interventional part.

1.5. Randomization and Blinding

Central randomization is implemented in this study. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject. Eligible subjects will be randomized 1:1 to receive either JNJ-53718678, or placebo.

Randomization will be based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

The randomization will be balanced by using randomly permuted blocks and will be stratified by time from randomization since the ARI alert (<24 hours versus ≥24 hours).

1.6. Observational and Interventional Study Stages

This study consists of two stages: (1) Observational stage, (2) Interventional stage. Two different sets of analysis datasets (interventional datasets and observational datasets) will be created. Throughout this SAP, definitions and analyses for the interventional stage will be covered in Sections 2 to 7. The definitions and the analyses for the observational stage will be covered in Section 8 of this SAP.

2. GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.3 (or higher). Graphical presentations are performed using SAS® version 9.3 (or higher) or R version 3.6.0 (or higher).

2.1. Visit Windows and Phase Definitions

2.1.1. Phase Definitions

Analysis phases for the interventional stage will be constructed as defined in Table 1.

Table 1: Analysis Phases for Subjects in the Interventional Stage

Analysis Phase [number]	Start Date/Time	End Date/Time
Observational [0]	00:00 of the date of signing the informed consent form for the observational stage	23:59 of the date before date of signing the informed consent form for the interventional stage
Screening [1]	00:00 of the date of signing the informed consent form for the interventional stage	1 minute before the first study drug administration in the trial
Treatment [2]	Date/time of first study drug administration in the trial	23:59 of the last day of treatment + 3 days or 23:59 of the cut-off date for the IA, whichever comes first
Follow-up [3]	1 minute after the End of Treatment 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

Assessments will be assigned to phases based on their datetime, 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 (except for adverse Events see details in section 2.4). 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.

2.1.2. Baseline

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

- For RSV RNA viral load:
  - Last available assessment within the 24h 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.
- For ePRO, the baseline assessment will be defined as:
  - 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.

2.1.3. Relative Day

In the interventional stage, Study Day 1(reference date) is defined as the date of first study medication intake.

All efficacy and safety assessments at all visits will be assigned a day relative to this date.

The relative day will be defined as:

$$reldy = visit\ date - reference\ date + 1$$

for visits on or after Day 1, and

$$reldy = visit\ date - reference\ date$$

for visits before Day 1. There is no ‘Day 0’.

2.1.4. Analysis Windows for Analysis Visits and Time Points

The visit windows and the target days are defined for each visit of the protocol.

In general, the following rules will be applied in order to have only one evaluation per subject per analysis visit:

- If two or more assessments fall within the same visit window, the measurement closest to the target day will be used (the time of the assessment will be ignored, only the date component will be used)
- If two assessments are equidistant, the last measurement within the interval will be 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:

- *Viral Load*

  For the analyses of RSV RNA viral load (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 RSV RNA viral load per day (regardless of sample collection setting [on-site vs homebased] and time of collection). The maximum RSV RNA viral load on a day will be used in all subsequent RSV RNA viral load analyses (e.g. time to undetectable) and for analysis visit windowing. Identified RSV RNA viral load, as assigned per analysis visit based on these rules, will be used for all subsequent by-visit RSV RNA viral load analyses.. Please notice that baseline viral load follows the rules described in Section 2.1.2.

- *Electrocardiogram*

  In case there is more than one triplicate ECG per analysis visit window, the following rule will be used to have only one evaluation per analysis timepoint:
  - The average of the last available complete ECG triplicate within the window, should be considered in first instance except for Day 1 and Day 3.
  - Day 1 and Day 3 measurements closest to 1h post dose will be used.
  - In absence of complete triplicate ECGs, the average of the last available ECG duplicate should be considered. For duplicates ECGs the same rule applies as for triplicates above.
  - In absence of complete or partial triplicates, the last available single ECG can be used.

Once baseline is assigned, any assessment performed prior to the defined baseline, will be assigned to Screening or observational. Observational stage and 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 viral load and ECG/laboratory assessments are defined as in Table 2.

Table 2: Visit Windows

Analysis Visit [scheduled Analysis Visit No.]	TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)]		
	VL	ECG	Laboratory
Baseline^ [0]	<=1 [1]	<=1 [1]	<=1 [1]
Day 1 [1]		>1 [1]	
Day 2 [2]	>1 to 2 [2]		
Day 3 [3]	3 [3]	3 [3]	
Day 4 [4]	4 [4]		
Day 5 [5]	5 [5]		
Day 6 [6]	6 [6]		
Day 7 [7]	7 [7]		
Day 8 [8]	8 [8]	8-9 [8]	8-9 [8]
Day 9 [9]	9 [9]		
Day 10 [10]	10 [10]		
Day 11 [11]	11 [11]		
Day 12 [12]	12 [12]		
Day 13 [13]			
Day 14 [14]	13-15 [14]		13-15[$] [14]
Day 15 [15]			
Day 16 [16]			
Day 17 [17]			
Day 18 [18]			
Day 19 [19]			
Day 20 [20]			
Day 21 [21]	18-24 [21]	18-24 [21]	
Day 22 [22]			
Day 23 [23]			
Day 24 [241]			

Table 2: Visit Windows

Analysis Visit [scheduled Analysis Visit No.]	TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)]		
	VL	ECG	Laboratory
Day 25 [25]			
Day 26 [26]			
Day 27 [27]			
Day 28* [28]		25 to +∞ [28]	25 to +∞ [28]

^ Baseline is defined as the last measurement before first study drug intake. Please also see Section 2.1.2
$ Will only be performed in case of any clinically significant laboratory abnormality observed at Day 8
* At the discretion of the investigator

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.

PRESORS ClinRO, Clinical evaluation and PRESORS ObsRO are collected as per Table 3. The assessments are performed either BID or QD.

Table 3: Planned Collection of PRESORS ClinRO, PRESORS ObsRO and Clinical Evaluation

Assessments	Hospitalized patients		Outpatients
	During Hospitalization	After Discharge	
PRESORS ClinRO	BID from Day 1 to Day 14 and QD from Day 15 to Day 21	Once at clinic visits	Once at clinic visits
Clinical Evaluation£/ SBP+DBP	BID from Day 1 to Day 21 + Day 28	Once at clinic visits + Day 28*	Once at clinic visits + Day 28*
PRESORS ObsRO	BID from Day 1 to Day 14 and QD from Day 15 to Day 21		
Body Temp Caregiver	NA	BID from Day 2 to Day 14 and QD from Day 15 to Day 21	BID from Day 1 to Day 14 and QD from Day 15 to Day 21

£ Clinical evaluation includes respiratory rate, heart rate, body temperature, and SpO2.
*only in case of on-site visit

Visit windows for these assessments are defined as in Table 4.

Table 4: Visit Windows for PRESORS ClinRO, PRESORS ObsRO, Clinical Evaluation (including SBP/DBP) and Body Temperature

Analysis Time	Time Interval	Target Time
Baseline		0
12h (Day 1.5)	>0h$; 17h59min	12h
24h (Day 2.0)	18h; 29h 59 min	24h
36h (Day 2.5)	30h; 41h 59min	36h

Table 4: Visit Windows for PRESORS ClinRO, PRESORS ObsRO, Clinical Evaluation (including SBP/DBP) and Body Temperature

Analysis Time	Time Interval	Target Time
48h (Day 3.0)	42h; 53h 59min	48h
60h (Day 3.5)	54h; 65h 59min	60h
72h (Day 4.0)	66h; 77h 59min	72h
84h (Day 4.5)	78h; 89h 59min	84h
96h (Day 5.0)	90h; 101h 59min	96h
108h (Day 5.5)	102h; 113h 59min	108h
120h (Day 6.0)	114h; 125h 59min	120h
132h (Day 6.5)	126h; 137h 59min	132h
144h (Day 7.0)	138h; 149h 59min	144h
156h (Day 7.5)	150h; 161h 59min	156h
168h (Day 8.0)	162h; 173h 59min	168h
180h (Day 8.5)	174h; 185h 59min	180h
192h (Day 9.0)	186h; 197h 59min	192h
204h (Day 9.5)	198h; 209h 59min	204h
216h (Day 10.0)	210h; 221h 59min	216h
228h (Day 10.5)	222h; 233h 59 min	228h
240h (Day 11.0)	234h; 245h 59min	240h
252h (Day 11.5)	246h; 257h 59min	252h
264h (Day 12.0)	258h; 269h 59min	264h
276h (Day 12.5)	270h; 281h 59min	276h
288h (Day 13.0)	282h; 293h 59 min	288h
300h (Day 13.5)	294h; 305h 59min	300h
312h (Day 14.0)	306h; 317h 59min	312h
Day 15	Day [15] (2 AM-1:59 AM)	15
Day 16	Day [16] (2 AM-1:59 AM)	16
Day 17	Day [17] (2 AM-1:59 AM)	17
Day 18	Day [18] (2 AM-1:59 AM)	18
Day 19	Day [19] (2 AM-1:59 AM)	19
Day 20	Day [20] (2 AM-1:59 AM)	20
Day 21	Day [21] (2 AM-1:59 AM)	21
Day 22	Day [22] (2 AM-1:59 AM)	22
Day 23	Day [23] (2 AM-1:59 AM)	23
Day 24	Day [24] (2 AM-1:59 AM)	24
Day 28	Day [25, +∞] (2 AM-1:59 AM)	28

[$] post baseline

From Day 15 onwards, relative day (adjusted by timeframe as in the table) will be used to define analysis visits. In case there is more than one assessment per analysis visit, the one closest to the target will be used for the summary table per analysis visit. If more than one is equally close, then the last one will be considered in the analysis.
Note: in case there is an assessment on Day 14 not covered in the 312h window, it will not be used in summary tables and figures but will only be shown in individual listings and figures.

For analyses for which we need at most one assessment per day (e.g., for summarizing combined in- and outpatient data captured by the clinician), we take the worst over 24 hours according to Table 5.

Table 5: Worst per Day

Analysis time	Primary Selection (worst hourly)	Secondary Selection* (worst daily) TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)]
Baseline		
Day 2	Worst [12h; 24h]	
Day 3	Worst [36h; 48h]	3 [3]
Day 4	Worst [60h; 72h]	
Day 5	Worst [84h; 96h]	4-6 [5]
Day 6	Worst [108h; 120h]	
Day 7	Worst [132h; 144h]	
Day 8	Worst [156h; 168h]	8-9 [8]
Day 9	Worst [180h; 192h]	
Day 10	Worst [204h; 216h]	
Day 11	Worst [228h; 240h]	
Day 12	Worst [252h; 264h]	
Day 13	Worst [276h; 288h]	
Day 14	Worst [300h; 312h]	13-15 [14]
Day 15	Worst as per relative day (2 AM-1:59 AM) Relative day	
Day 16		
Day 17		
Day 18		
Day 19		
Day 20		
Day 21		18-24 [21]
Day 28	25 to +∞ [28]	25 to +∞ [28]

Note: For ClinRO and Clinical Evaluation **only**: the secondary selection approach will be considered in the analysis **if** no record is assigned to Day 3, Day 5, Day 8, Day 14 and/or Day 21 according to the rules in the primary selection column in Table 5 (for hospitalized subjects after discharge, or for outpatientss).

- If worst per day as per primary selection available, same value will be assigned for the secondary selection of worst per day.
- Otherwise, worst per day as per secondary selection will be derived considering all possible values within the relative day window. The worst possible result will be selected regardless of being the closest one to the target day.

Day 28 will always be assigned according to the window "25 to +∞". The primary and secondary selection for Day 28 will be identical as the same interval is used for both.

2.2. Pooling Algorithm for Analysis Centers

As the primary endpoint is a laboratory assessment (objective endpoint) evaluated by a central assay, no heterogeneity of treatment effects across centers is expected. No pooling algorithm for analysis centers will be applied.

2.3. Analysis Sets

2.3.1. All Enrolled Analysis Set

All participants who signed the ICF of the interventional stage.

2.3.2. All Randomized Analysis Set

All subjects who were randomized in the interventional stage of the study regardless of being treated or not.

2.3.3. Efficacy Analysis Set(s)

The Intent-To-Treat-infected (ITT-i) set will be used to perform the evaluation of all efficacy variables including clinical course endpoints. The primary endpoint (viral load) and key clinical course endpoints (time to resolution of all RSV symptoms, rate of complications, overall RSV severity score) might also be analyzed on the Per Protocol (PP) set.

2.3.3.1. ITT-i Set

All randomized subjects who received at least one dose of study drug and who have a centrally confirmed RSV viral load of ≥1 $\log_{10}$ copies/mL above the lower limit of quantification (LLOQ) of the RSV RT-qPCR assay at baseline. Analyses on the ITT-i set will be performed as randomized.

2.3.3.2. PP Set

All subjects in the ITT-i analysis set with the exclusion of any subject with protocol deviations deemed to have a major impact on the assessment of efficacy. The subjects to be excluded will be identified and documented prior to database lock based on the following criteria:

- Entered but did not satisfy criteria, violation of:
  - inclusion criteria 1 or 6 (interventional stage)

    AND/OR
  - exclusion criteria 2, 5, 9 (from the interventional stage) and 4, 5 (from the observational stage)

Please see Sections 5.1 and 5.2 of the protocol for full description of the criteria.

- Received wrong treatment or incorrect dose
  - The actual treatment not the same as the planned treatment
  - Subjects missed more than 1 dose (if the subject was randomized before Protocol amendment 2) or 2 doses (if the subject was randomized after Protocol amendment 2) (including subjects who discontinued the study medication earlier)

- Other:
  - Unplanned unblinding has taken place during the study

  - Insufficient post-baseline viral load samples collected (should have at least baseline and 2 post dose samples between Day 2 and Day 5)

- Received concomitant treatment that may affect the efficacy of the trial medication. Complete list of concomitant medications to be considered for major protocol violation will be identified and documented before the database lock.

- Missing PRESORS ObsRO:
  - at baseline
  - >1 missing for 5 consecutive assessments during BID schedule
  - >1 missing for 4 consecutive assessments during QD schedule

Note that in the PP set subjects will be treated as randomized (by definition). Analyses on the PP set will only be performed if at least 4 subjects in the ITT-i set are excluded for the PP set.

2.3.4. Safety Analysis Set

2.3.4.1. Safety Set

The Safety set includes all subjects who received at least 1 dose of study drug, and will be analyzed as treated, regardless of the randomized treatment group assigned. Where 'analyzed as treated' is defined as:

- Placebo: if only placebo doses received
- JNJ-53718678: if at least one dose of the active study drug received

The Safety set will be used to perform the evaluation of all safety variables and will be used for listings.

2.4. Definition of Subgroups

The following subgroups will be investigated for efficacy, including the primary endpoint (viral load) and key clinical course endpoints (time to resolution of all RSV symptoms, rate of complications, overall RSV severity score). For safety, no subgroup analyses will be done. See Table 6.

Table 6: Subgroup definitions

Subgroup	Definition
Symptom Onset	• Subjects with symptom onset ≤3 days before randomization • Subjects with symptom onset >3 days before randomization
RSV Viral Subtype	• RSV A • RSV B • RSV A+B

Further subgroup analyses might be performed for the efficacy data if it seems useful to be combined with the RSV2002 data.

2.5. Definition Treatment group

Two treatment schedules were used in this study, QD schedule implemented before protocol amendment 2 and BID schedule implemented after amendment 2 but with similar total daily doses. Treatment group will be defined based on the total daily dose.

2.6. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of first dosing of the study medication
  - The day of first dosing of the study medication, if the month/year of the onset of AE is the same as month/year of the first dosing of the study medication and month/year of the AE resolution date is different
  - The day of first dosing of the study medication or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dosing of the study medication and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first dosing of the study medication
  - Month and day of the first dosing of the study medication, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the first dosing of the study medication,
  - The AE resolution date.

Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set to the earlier of:
  - 00:01 as long as the onset date is after the first dosing of the study medication
  - The time of the first dosing of the study medication if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Unplanned interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities. In case of an interim analysis, investigators, participants' parents/caregivers, and local sponsor representatives will remain blinded. The sponsor leadership team responsible for decisions and the central study team required to generate and interpret results will have access to unblinded data.

An IDMC will be commissioned for this study to monitor and review data for the interventional stage in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this stage. The committee will meet periodically to review safety data. After the review, the IDMC will provide recommendations to the Sponsor Committee. At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or to the safety assessments to the Sponsor Committee to ensure the safety of enrolled participants.

The IDMC will consist of at least one pediatrician, at least one medical expert in infectious diseases, and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter. A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making, considering the IDMC recommendations, and will communicate these decisions to the study team. The IDMC of this study also functions as the IDMC for 53718678RSV2002 and the meetings are combined for both studies. Details are provided in the IDMC Charter.

4. SUBJECT INFORMATION

All subject information analyses described in the following sections will be done on the ITT-I set and safety set, unless otherwise for specific display (in the data presentation specification (DPS) document). Subject information will be summarized by treatment group and overall.

4.1. Demographics and Baseline Characteristics

Table 7 and Table 8 presents demographics and baseline characteristics respectively that will be summarized descriptively by treatment group, and overall. Demographics and baseline characteristics will also be summarized by subgroup if appropriate.

Table 7: Demographics

Continuous Variables:	**Summary Type**
Age at randomization (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight at baseline (kg)	
Length/Height at baseline (cm)	
Head Circumference at baseline (cm)	
Categorical Variables	Counts (n, %)
Sex (male, female, unknown, undifferentiated)	
Age Group (≥28 days and <3 months, ≥3 months and <6 months, ≥6 months)	
Ethnicity[a] (Hispanic or Latino, Not Hispanic or Latino, Not Reported)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not Reported)	
Country	
Setting (Hospitalized, Outpatient)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'. The specifications of the categories 'Other' and 'Multiple' will only be listed.

Table 8: Baseline Characteristics

Continuous Variables:	**Summary Type**
Duration of RSV symptoms prior to ARI visit (days)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Duration of RSV symptoms prior to randomization (days)	
RSV Viral Load (log_{10} copies/ml)	
RSV Viral Load (log_{10} copies/ml) by RSV Subtype	
RSV Viral Load (log_{10} copies/ml) by symptom onset	
RSV Viral Load (log_{10} copies/ml) by RSV Subtype and by symptom onset	
Respiratory Rate (breaths/min)	
Heart Rate (beats/min)	
Oxygen Saturation (%) at baseline	
Number of other siblings within the household	
Categorical Variables	Counts (n, %)
RSV Subtype (RSV A, RSV B, RSV A+B)	
Time from ARI alert to randomization (<24 hours, ≥24 hours) (as derived from CRF)	
Symptom onset (≤3 days, >3 days) at randomization	
Presence of risk factors for severe RSV disease (no, yes)	
Receiving Supplemental Oxygen prior to first intake of study medication (no, yes)	
Prenatal Smoking by the subject's mother (no, yes)	
Exposed to tobacco smoke in home environment (no, yes)	
History of atopy/allergy (no, yes)	
Contact with other children (siblings, Kindergarten, daycare) (no, yes)	
Mode of delivery (vaginal, C-section, not documented)	
Feeding type (only breast milk, only formula, combination breast milk and formula, solid food only, solid food combined with milk/formula)	
Currently attending daycare (no, yes) If yes, days per week (1, 2, 3, 4, 5, 6, 7) If no, will child attend day care in the future (yes, no)	
Received palivizumab (no, yes)	
Received aerosolized ribavirin (no, yes)	

Table 8: Baseline Characteristics

Continuous Variables:	Summary Type
Received IV immunoglobulin (no, yes)	
Presence of respiratory bacteria (no, yes)	
Presence of other respiratory viruses (no, yes) *	

*Viral and bacterial respiratory co-pathogens are detected in a baseline nasal mid-turbinate swab sample using the Pathofinder Respifinder. 2 SMART assays (allows for detection of Influenza A virus, Influenza A virus H1N1 pdm2009, Influenza B virus, human respiratory syncytial virus A, human respiratory syncytial virus B, human metapneumovirus, rhinovirus/enterovirus, adenovirus, human parainfluenza virus 1, human parainfluenza virus 2, human parainfluenza virus 3, human parainfluenza virus 4, bocavirus, coronavirus NL63/HKU1, coronavirus 229E, coronavirus 0C43, severe acute respiratory syndrome coronavirus 2, and Middle East respiratory syndrome coronavirus, Chlamydophila pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, and Bordetella pertussis), the Fast Track Diagnostics Bacterial pneumonia_CAP assay (CAP1, allows for detection of Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and Moraxella catarrhalis), and the Fast Track Diagnostics Bordetella assay (allows for detection of Bordetella pertussis and Bordetella parapertussis).

4.2. Disposition Information

The number of screened subjects and reasons for screen failures will be summarized.
Summaries will be provided for the following disposition information:

- Randomized, randomized and treated, Safety set, ITT-I set and PP set
- Number of subjects who completed and discontinued treatment and the trial, with a breakdown of the reasons for discontinuation.

4.3. Treatment Compliance

Treatment compliance will be calculated as follows:

Treatment compliance (%) = 100 x number of doses of study medication / planned number of doses according to the protocol (7 or 14 doses, depending on the time the subject was randomized [before or after Protocol amendment 2]).

Dosing compliance will be summarized descriptively by treatment group. The reasons for not administered doses will be listed.

4.4. Protocol Deviations

All major protocol deviations will be listed. Those that may affect the assessment of efficacy will be flagged (see Section 2.3.3.2).

4.5. Medical History and Family History

The medical history and family history records will be listed.

4.6. Prior and Concomitant Medications

Medications taken from the date when the ICF (for the interventional stage) is signed through the end of study will be summarized by setting, by treatment group, overall, and by preferred term using the World Health Organization-Drug Dictionary as frequency tables for the prior and concomitant medications separately:

1. Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended.

2. Concomitant medication: medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication. The part on concomitant medication will be shown by ATC class level up to level 3. If a prior/concomitant therapy record misses components of its start and/or stop dates (time and/or day and/or month and/or year), the following actions will be taken:

1. In case of partial start or stop datetimes, the concomitant therapy records will be allocated to prior/concomitant using the available partial information, without imputations.

2. In case of a completely missing start date, the prior/concomitant therapy will be considered as having started before the trial.

3. In case of a completely missing end date, the prior/concomitant therapy will be considered as ongoing at the end of the trial.

All prior and concomitant medication will be listed.

4.7. Presence of Other Respiratory Viruses or Bacteria

Data on other respiratory viruses or bacteria, determined by multiplex PCR in mid-turbinate nasal swabs collected at baseline will be listed. Proportions of positive and negative results will be tabulated.

5. EFFICACY

All efficacy endpoints will be analyzed on the ITT-i set (interventional stage of the study).
The efficacy analyses include the following primary, secondary, and exploratory endpoints.

Primary Endpoint

The primary efficacy endpoint is the RSV viral load AUC from immediately prior to first dose of study drug through Day 5 derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs.

Secondary Endpoints

- virologic parameters derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs including:
  - RSV viral load and change from baseline over time
  - RSV viral load AUC from immediately prior to first dose of study medication (baseline) through Day 3 and Day 8.

  - time to undetectable RSV viral load
  - proportion of participants with undetectable RSV viral load at each time point throughout the study

- clinical course related endpoints:

  The following endpoints will be based on the PRESORS assessed throughout the interventional stage of the study by parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) and by the investigator (clinician PRESORS) during scheduled visits:

    - duration and severity of signs and symptoms of RSV disease assessed throughout the study by parent(s)/caregiver(s) PRESORS and by clinician PRESORS
    - change from baseline in parent(s)/caregiver(s) PRESORS (worsening or improvement)
    - change from baseline in clinician PRESORS (worsening or improvement)
    - time to resolution (ie, to none or mild) of RSV symptoms
    - time to improvement based on general questions on overall health
    - proportion of participants with improvement or worsening of RSV disease based on general questions on overall health on each study day from screening till Day 21
    - time to return to pre-RSV health as rated by the parent(s)/caregiver(s)
    - respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2) over time as measured during scheduled visits
    - need for (re)hospitalization during treatment and follow-up

- safety and tolerability, as assessed by AEs, clinical laboratory testing, ECGs, and vital signs, throughout the interventional stage of the study
- Due to limited number of subjects at the end of the study, no modelling will be done. Individual PK concentrations will be listed

Exploratory Endpoints

Due to the limited number of subjects at the end of this study not all exploratory endpoints will be analyzed. Below are the exploratory endpoints that will be analyzed.

- changes from baseline in the RSV F-gene sequence (and potentially other regions of the RSV genome, at the discretion of the sponsor's virologist)
- the occurrence of complications with onset after treatment initiation that are associated with RSV disease per investigator assessment:
  - bacterial superinfections (eg, pneumonia, sinusitis, bronchitis, bacteremia of presumed respiratory origin per investigator assessment)
  - otitis media, bronchiolitis, viral pneumonia
  - exacerbations of underlying pulmonary disease (eg, asthma, cystic fibrosis, bronchopulmonary dysplasia)

– exacerbations of underlying cardiovascular conditions

5.1. Hypothesis

The primary hypothesis of the interventional stage is that JNJ-53718678 has antiviral activity against RSV as assessed by a reduction in RSV viral load AUC (from immediately prior to first dose of study medication [baseline] until Day 5) at the 5% level (one-sided) for JNJ-53718678 compared to placebo in participants recruited from birth.

5.2. Analysis Specifications

The randomization stratification factor (time between ARI alert and randomization [<24 hours or ≥24 hours]) as derived from CRF will be used in the efficacy analyses.

5.2.1. Level of Significance

The primary endpoint will be tested at alpha level of 5% (one-sided).

5.2.2. Data Handling Rules

Viral Load

Rule of maximum: Before any imputation is applied, the value for each Day is defined as the maximum value of all RSV viral load assessments performed on that day. Please notice that this rule doesn't apply for baseline. For baseline details please see Section 2.1.2.

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 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) (i.e., 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 subject 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 (i.e. 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 $\log_{10}$.

5.3. Primary Efficacy Endpoint(s)

5.3.1. Definition

RSV viral load will be measured in mid-turbinate nasal swab specimens using an RSV-A/B qRT-PCR assay.

The primary efficacy endpoint is the RSV viral load area under the curve (AUC) from immediately prior to first dose of study drug (baseline) through Day 5 ($AUC_{Day\ 1\text{-}5}$) derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs.

5.3.2. Analysis Method

The primary estimates of the RSV viral load $AUC_{Day1\text{-}5}$ will be derived from a mixed model. No explicit imputations of missing data from post-baseline nasal swabs will be done in this model, as this mixed model would allow to make inferences implicitly imputing the missing data under the missing at random assumption.

Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood based repeated measures approach. The analysis model includes fixed effect parameters for treatment, randomization stratification factor, analysis visit, and treatment-by-analysis visit interaction, as well as continuous covariates for baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load-by-analysis visit interaction. An unstructured covariance structure will be selected. In case this model doesn't converge, the Toeplitz covariance structure will be applied. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The differences between the AUCs will be estimated using appropriate contrasts. The primary null hypothesis of worse or no treatment effect will be rejected if the RSV viral load $AUC_{Day1\text{-}5}$ is significantly lower than placebo using a one-sided test at the 0.05 significance level.

For subgroup analysis, the model will be applied per subgroup.

5.4. Secondary Endpoints

5.4.1. Definitions

Formulae to be used for derived variables, including data conversions, are provided in the tables below. Note that for time-to event variables the actual date times will be used.

5.4.1.1. RSV RNA Viral Load (qRT-PCR)

Definitions for the derived viral load parameters are provided in Table 9.

Table 9: Viral Load Parameters

Measurement	Formula
Log_{10} viral load actual values	Log_{10} 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
Time to virus undetectable (hours) [Time-to event]	Time to virus undetectable will be evaluated as below: The time in hours from initiation of study treatment until the first post-baseline time point at which the virus is confirmed undetectable (= event). A confirmed undetectable sample is defined as the first of at least two consecutive samples that are undetectable. The last obtained sample for a subject , if undetectable is considered confirmed. **Situation** / **Censoring** Last record is baseline assessment / time 0h Last available assessment is detectable / (right censored) at last available assessment (Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal.
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 detectable 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)

Additionally, AUC_{Day1-3} and AUC_{Day1-8} will be analyzed using a mixed model approach (see Section 5.3.2).

5.4.1.2. Paediatric RSV Electronic Severity and Outcome Rating System (PRESORS)

This study includes version 7.1 of the PRESORS.

The ObsRO scoring system that will be used during this study is available in Attachment 2: PRESORS ObsRO Scoring System. The ClinRO scoring system that will be used during this study is available in Attachment 3: PRESORS CLINRO Scoring System. Some PRESORS parameters were modified and will be derived as provided in Table 10.

5.4.1.2.1. PRESORS Modified Definitions

Based on the PRESORS validation results of 64041575RSV0001 study and the IA of 53718678RSV2002 (data cut-off 02JAN2020), modified scores were defined implementing the following changes for concept scores and definition of resolution:

Table 10: PRESORS Modified Definitions

PRESORS	CONCEPT/ Answer level	ORIGINAL		MODIFIED	
		Score	Definition	Score	Definition
Caregivers (ObsRO)	**Dehydration** "Dry Skin or Lips"	2	Not Resolved	1	Resolved
	Retractions "Belly Sucked in while breathing"	1	Resolved	2	Not Resolved
	Cyanosis	Any	Any	Not considered	
	Apnea	Any	Any	Not considered	
Clinician (ClinRO)	**Retractions** "Subcostal Retractions"	1	Resolved	2	Not Resolved
	Cyanosis	Any	Any	Not considered	
	Apnea	Any	Any	Not considered	

PRESORS data will be analyzed as follows:

- Considering modified concepts scores and modified definition of resolution.
- The modified summary parameters for scores and time to resolution (Overall RSV Symptoms, Key RSV Symptoms, Respiratory Symptoms and General Illness Behavior) will be derived excluding Cyanosis and Apnea and using modified concepts scores and modified definition of resolution (Dehydration and Retractions for ObsRO and Retractions for ClinRO).

All the analyses will be based on the modified definitions.

Table 11: Parameters based on PRESORS

Measurement	Formula
PARENT/CAREGIVER PRESORS (ObsRO)	
ObsRO concept scores + change from baseline	Score per concept according to the score system provided in Attachment 2. Each concept score ranges from 0 to 3. The higher the score, the worse the symptom/concept.

Table 11: Parameters based on PRESORS

Measurement	Formula
ObsRO summary scores + change from baseline	Average of the different concepts, ranging from 0 to 3. Summary scores are key RSV symptom severity score, respiratory symptom severity score, general illness behavior and overall RSV severity score and will be calculated as defined in Attachment 2.
Daily summary scores	For each ObsRO summary score, a daily summary score will be calculated as follows: **Average of the worst**: daily summary score will be the average of the worst score reached per concept. Table Worst per Day (see Table 5) timepoints will be applied and as a result "worst hourly" and "worst daily" will be calculated. Please notice that unless otherwise stated, the daily summary score "worst hourly" is the one considered in the analyses.
Time to resolution of all RSV symptoms (hours) [Time-to event]	Time (in hours) from first dose of study drug until the first time of resolution of all RSV Symptoms (concepts from ObsRO). Symptoms/Concepts are sleep disturbance, crying, illness behavior, breathing problems, retractions, tachypnea, breathing sounds, cough, nasal secretions, tachycardia, feeding, dehydration. Cyanosis and apnea will not be considered when modified definitions applied. Resolution occurs when all symptoms from the ObsRO are scored as none or mild (score of 0 or 1, respectively) for at least 24 hours. • **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 should have been done over 3 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed In case RSV symptoms are not resolved, data will be censored. Censoring will be done as follows: **Situation** / **Censoring** Last record(s) indicate resolution of RSV symptoms **but** insufficient recordings to meet the time to resolution / first record of resolution from the last series of recordings of resolution of RSV symptoms Last record does **not indicate resolution** of RSV symptoms / after the last observation, at 20:00 on the same day **if the last observation was a morning** diary entry (from 2:00 until 13:59)

Table 11: Parameters based on PRESORS

Measurement	Formula
	<table><tr><td></td><td>at 8:00 the next day if the **last entry was an evening** diary (from 14:00 until 01:59). In case the assessment was between 00:00 and 01:59, they will be censored at 08:00 that same day</td></tr><tr><td>Death (without previous resolution)</td><td>date/time of death</td></tr><tr><td>missing information to determine resolution of symptoms because of hospitalization</td><td>date/time of hospitalization</td></tr></table> (Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
Time to resolution of key RSV symptoms (hours) [Time-to event]	Time (in hours) from first dose of study drug until the first time of resolution of key RSV symptoms. Concepts are breathing problems, retractions, tachypnea, breathing sounds, , cough and tachycardia. Cyanosis and apnea will not be considered when modified definitions applied. Resolution occurs when all key RSV symptoms from the ObsRO are scored as none or mild (score of 0 or 1, respectively) for at least 24 hours. Similar rules as for time to resolution of all RSV symptoms will be applied.
Time to resolution of respiratory symptoms (hours) [Time-to event]	Time (in hours) from first dose of study drug until the first time of resolution of respiratory symptoms. Concepts are breathing problems, retractions, tachypnea, breathing sounds, cough, tachycardia and nasal secretions. Cyanosis and apnea will not be considered when modified definitions applied. Resolution occurs when all respiratory symptoms from the ObsRO are scored as none or mild (score of 0 or 1, respectively) for at least 24 hours. Similar rules as for time to resolution of all RSV symptoms will be applied.
Time to resolution of general illness behavior symptoms (hours) [Time-to event]	Time (in hours) from first dose of study drug until the first time of resolution of general illness behavior symptoms (5 general illness behavior concepts from ObsRO). Concepts are sleep disturbance, crying, illness behavior, feeding and dehydration. Resolution occurs when all general illness behavior symptoms from the ObsRO are scored as none or mild (score of 0 or 1, respectively) for at least 24 hours. Similar rules as for time to resolution of all RSV symptoms will be applied.
Status of RSV symptoms at each time point (categorical)	Each assessment of 'Keeping in mind all the symptoms you observed ***[recall period]***, overall, how would you rate the child's RSV symptoms now?' will be assigned to one of the 6 categories below: □ None □ Very mild □ Mild □ Moderate □ Severe

Table 11: Parameters based on PRESORS

Measurement	Formula
	□ Very severe
Status of health at each time point (categorical)	Each assessment of '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 improvement of RSV symptoms at each time point (categorical)	Each assessment of 'Would you say the child's RSV symptoms have improved, are about the same or are 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
Time to improvement of RSV symptoms (general question) [Time-to-event]	Time (in hours) from first dose of study drug until first time status of improvement of RSV symptoms reported as "very much improved" or "much improved" based on response to question 'Would you say the child's RSV symptoms have improved, are about the same or are worse than when the child entered the study? Similar rules as for time to resolution of all RSV symptoms will be applied.
Status of return to pre-RSV disease health at each time point (binary)	Each assessment of 'Has the child's health returned to normal (how it was before RSV)?' will be assigned to one of the 2 categories below: □ No □ Yes
CLINICIAN PRESORS (ClinRO)	
ClinRO concept scores + change from baseline	Score per concept according to the score system provided in attachment 3. Each concept score ranges from 0 to 3. The higher the score, the worse the symptom/concept.
ClinRO summary scores + change from baseline	Average of the different concepts, ranging from 0 to 3. Summary scores are key RSV symptom severity score, respiratory symptom severity score, general illness behavior and overall RSV severity score and will be calculated as defined in attachment 3.
ClinRO daily summary scores	For each ClinRO summary score, a daily summary score will be calculated as follows: **Average of the worst:** daily summary score will be the average of the worst score reached per concept. Table Worst per Day (see Table 5) timepoints will be applied and as a result

Table 11: Parameters based on PRESORS

Measurement	Formula
	"worst hourly" and "worst daily" will be calculated. Please notice that unless otherwise stated, the daily summary score "worst daily" is the one considered in the analyses.
Status of overall condition at each ime point (categorical)	Each assessment of '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 '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:*** With respect to the child's RSV infection, how would you describe the child's health now compared to the baseline assessment? Ordinal scale from -5 to 5 where -5 indicates 'very much worse', 0 indicates 'unchanged', and 5 indicates 'very much better'

5.4.1.3. Other Clinical Course Parameters

5.4.1.3.1. Respiratory Rate, Heart Rate, Oxygen Saturation and Body Temperature

Definitions to be used for derived clinical course vital signs parameters are provided in Table 12.

Table 12: Clinical Course Vital Signs Parameters

Measurement	Formula
Respiratory Rate (RR) actual values + changes from baseline	RR as measured by the investigator during scheduled visits *change = (observed post-baseline RR – baseline RR)*
Heart Rate (HR) actual values + changes from baseline	HR as measured by the investigator during scheduled visits *change = (observed post-baseline HR – baseline HR)*
Oxygen Saturation (SpO_2) actual values + changes from baseline	Oxygen Saturation as measured by the investigator during scheduled visits
Body Temperature (clinician) actual values + changes from baseline	Body Temperature as measured by the investigator during scheduled visits *Change = (observed post-baseline temperature – baseline temperature)*
Body Temperature (caregiver) actual values + changes from baseline	Body Temperature as measured at home *Change = (observed post-baseline temperature – baseline temperature)*

5.4.2. Endpoint-specific analysis methods

5.4.2.1. RSV RNA Viral Load (qRT-PCR)

Log_{10} Viral Load

Descriptive statistics mean (SE) graphs and median (IQR) graphs will be shown for the log_{10} viral load actual values and changes from baseline by analysis visit and by treatment group. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 90% confidence interval, median, range and interquartile range. Descriptive statistics will be presented overall, and by subgroup (as defined in Section 2.4).

Differences on RSV RNA log_{10} viral load by qRT-PCR between treatment groups and by analysis visit will be determined using appropriate contrasts in a similar mixed effects model as the one used for the primary endpoint (see Section 5.3.2). The 90% 2-sided confidence intervals will be presented.

RSV viral load AUC

A similar model as used for the primary analysis will be used for the viral load AUC through Day 3, and through Day 8. The differences in these AUCs for treatment group versus placebo group will be derived using appropriate contrasts for both through day 3 and through day 8 and from the same model containing all RSV RNAS viral load assessment from baseline through Day 8. Least squares mean estimates of treatment differences, including the 90% 2-sided confidence intervals.

For subgroup analyses, the model also will be applied per subgroup. For details about subgroups refer to Section 2.4.

Proportion of subjects with undetectable RSV viral load

The proportion of subjects within the RSV RNA viral load categories (undetectable, detectable and quantifiable) will be shown in a frequency tabulation, as well as graphically, by treatment group and analysis visit. Subjects 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.

Time to virus confirmed undetectable [time-to event]

This time-to event variable will be analyzed using Kaplan-Meier analysis (for time to confirmed undetectable). A summary table including number of subjects included in the analysis, number of subjects censored, 25^{th} and 75^{th} percentiles and median time-to event, with confidence intervals based on log-log transformation method, will be presented by treatment group. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by treatment. For subgroup analysis, Kaplan-Meier plots will be produced per subgroup.

5.4.2.2. Paediatric RSV Electronic Severity and Outcome Rating System (PRESORS)

ObsRO concept, summary and daily scores; ClinRO concept, summary and daily scores

Descriptive statistics mean (SE) graphs, and median (IQR) graphs will be shown for the actual values and changes from baseline by visit and treatment group. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 90% two-sided confidence interval, median, range and interquartile range. Descriptive statistics will be presented overall, and by subgroup (as defined in Section 2.4). For analyses for which we need at most one assessment per day (e.g. for summarizing combined in- and outpatient data captured by the clinician), we take the worst over 24 hours according to Table 5. Graphical presentation of actual values and changes from baseline for individual concepts score and /or summary parameters (daily summary score[worst of the average]) over time include mean(SE) and Bar plots.

Time to resolution of all RSV symptoms, Time to resolution of key RSV symptoms, Time to resolution of respiratory symptoms, Time to resolution of general illness behavior symptoms (ObsRO)

These time-to event variables will be analyzed using Kaplan-Meier analysis. The 90% 2-sided confidence intervals will be presented. For subgroup analyses, Kaplan-Meier plots will be produced per subgroup.

Time to improvement of RSV symptoms (ObsRO general question)

These time-to event variables will be analyzed using Kaplan-Meier analysis. The 90% 2-sided confidence intervals will be presented.

Status of RSV symptoms, Status of health, Status of improvement of RSV symptoms, Status of return to pre-RSV disease health (ObsRO)

The proportion of subjects within the categories will be shown in a frequency tabulation, as well as graphically, per analysis time point (with corresponding 90% CIs), per treatment group and visit. Subjects with missing data on that analysis visit will not be counted in the denominator for the proportion.

Status of overall condition, Status of health, Health compared to the baseline assessment (ClinRO)

The proportion of subjects within the categories will be shown in a frequency tabulation, as well as graphically, per analysis time point (with corresponding 90% CI), per treatment group and visit. Subjects with missing data on that analysis visit will not be counted in the denominator for the proportion.

5.4.2.3. Other Clinical Course Parameters

5.4.2.3.1. Respiratory Rate, Heart Rate, Oxygen Saturation and Body Temperature

Descriptive statistics mean (SE) graphs and median (IQR) graphs will be shown for the actual values and changes from baseline by visit and by treatment group. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 90% 2-sided confidence interval, median, range and interquartile range.

For analyses for which we need one assessment per day (eg for summarizing combined in and outpatient data captured by clinician), we take the worst over 24 hours according to Table 5. For respiratory rate, heart rate and body temperature, the worst grade/value would be considered as the maximum value while for oxygen saturation, the lowest value will be considered the worst.

5.4.3. Definition

Table 13: Exploratory Parameters

Measurement	Formula

RSV-related complication (original definition)	Subjects who experienced RSV-related complication after first dose of study drug will receive code 1, subjects who did not experience a complication will receive code 0.
	
	The overall category will consist of any complication (answer to the question: "Is this AE a complication related to the current respiratory infection?").
	
	The following subcategories will also be analyzed:
	
	▪ Respiratory complications
	  o Bacterial complications
	  o Viral complications
	▪ Non-respiratory infectious complications
	  o Bacterial complications
	  o Viral complications
	▪ Other

RSV-related complication (modified definition)	Any subject who experienced at least one treatment emergent adverse event (TEAE) included in the list of complications below will receive code 1, subjects who did not experience any of the specified TEAE will receive code 0. • Respiratory complications: respiratory failure, respiratory distress, apneic attacks, bronchiolitis, bronchial obstruction, pneumonia, asthmatic crisis. • Infectious complications: otitis media, bacterial respiratory tract infections, sepsis. • Cardiovascular complications: arrhythmia, cardiogenic shock, hemodynamic instability, congestive cardiac failure. • Acid-base or electrolyte complications: metabolic acidosis (serum HCO_3^- <16), metabolic alkalosis (serum HCO_3^- >30)

Table 13: Exploratory Parameters

Measurement	Formula
	The list of TEAE to be considered as per modified definition of RSV-related complication, will be reviewed and documented prior to the final database lock. The modified definition for RSV-related complication will be the primary definition used in the analyses.

5.4.4. Analysis Methods

Respiratory Infection Complication

The proportion of subjects with a complication (yes and no) will be shown in a frequency tabulation.

6. SAFETY

All safety analyses will be descriptively summarized and based on the Safety set. There will be no formal statistical testing for any safety endpoint.

6.1. Adverse Events

6.1.1. Definitions

Coding of AE

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Events are looked at on the level of their preferred term.

Emergent Adverse Event

Emergent AEs are AEs with onset after first study medication intake or that are a consequence of a pre-existing condition that has worsened since baseline. All reported emergent AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Phase Allocation of AE

Adverse events present in the SDTM database are allocated to phases based on their start date. If the start date of an event falls between (or on) the start and stop date of a phase, the AE is attributed to that phase (emergent principle).

Incomplete dates (i.e. time and/or day and/or month and/or year missing) are imputed according to the rules in Section 2.5

6.1.2. Analysis Methods

Treatment-emergent adverse events will be summarized by body system, preferred term and treatment group.

A summary will be provided for the following emergent adverse events by phase (treatment phase and treatment phase + follow-up phase combined) and by treatment:

- any adverse events
- serious adverse events
- deaths due to AE
- adverse events by toxicity grade
- AEs at least possibly related to study medication
- AEs for which study medication was permanently stopped
- AEs for which study was discontinued prematurely
- serious adverse events that were at least possibly related to study medication.

Incidence tabulation will be provided for individual adverse events in the above categories (in case there are at least 2 events in any group)

In addition to the summary tables, the following listings will be provided for all subjects with: Any AEs, serious AEs, AEs leading to death, AEs leading to termination of study participation, severe AEs (grade 3-4 AEs).

The summary, incidence tabulation for the individual preferred terms and subject listing will be provided for the RSV-related complications.

The following adverse events will be tabulated or listed (in case there are less than 5 events); overall: any AE, any RSV-related complications, any grade 3-4 AE, AEs that are at least possibly related to study medication, AEs that have at least grade 2 and are at least possibly related to study medication, AEs leading to death, serious AEs, AEs leading to permanent stop of study medication and Cardiac events potentially related to QT prolongation (see Table 14) and Hepatobiliary Events (see Table 15)

Table 14: Cardiac Events Potentially Related to QT Prolongation

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 repolarization abnormality	10052464
Electrocardiogram U wave inversion	10062314
Electrocardiogram U wave present	10057913
Electrocardiogram U-wave abnormality	10055032
Loss of consciousness	10024855
Electrocardiogram QT interval abnormal	10063748
Sudden cardiac death	10049418
Sudden death	10042434
Syncope	10042772
Ventricular arrhythmia	10047281
Ventricular fibrillation	10047290
Ventricular flutter	10047294
Ventricular tachyarrhythmia	10065341

Table 15: Hepatobiliary Events

MedDRA Preferred Term (PT)	MedDRA Code
Drug-induced liver injury	10072268
Hyperbilirubinaemia	10020578
Jaundice	10023126
Ocular icterus	10058117
Yellow skin	10048245
Hepatitis, non-infectious	20000010
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

6.2. Clinical Laboratory Tests

6.2.1. Definitions

Laboratory parameters of hematology, serum chemistry, and urinalysis will be investigated: all analyses will be done on International System of Units (SI) converted values as available in the database.

Units:

The analysis of laboratory data will be done on standard international converted values only (Lbstresn/Lbstresu variable) except for GFR.

Estimation of GFR:

The local lab is to report the eGFR using the Schwartz formula [2]. In case the eGFR is not provided by the site the GFR will be estimated using the Schwartz method for pediatric subjects

$$eGFR = \frac{0.45 * height}{CRT\ [\frac{mg}{dL}]}$$

- Where eGFR = estimated Glomular Filtration Rate in mL/min/1.73m²
- height = subject height in cm at baseline of interventional stage
- CRT = serum creatinine in mg/dL.

  In case the creatinine is reported in umol/L in the SDTM, the following formula will be applied:

$$eGFR = \frac{0.00509 * height}{CRT\ [\frac{umol}{L}]}$$

Toxicity grades and abnormalities for laboratory parameters

The laboratory abnormalities will be determined according to the Division of Microbiology and Infectious Diseases (DMID) pediatric toxicity tables (see Attachment 1). Toxicity grades will be computed according to the DMID pediatric toxicity tables (version November 2007) and will be used in the analysis. In case no toxicity grades are defined for a test and /or age group, the abnormalities (above/below normal range) will be used.

In determining toxicity grades/abnormalities for each subject the following rules are applied:

- Worst grades/abnormalities are determined over the whole evaluation period, per phase (treatment, follow-up and combination treatment + follow-up), including unscheduled measurements.

- The abnormalities "abnormally low" and "abnormally high" are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)
- If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations.
- The eGFR will be calculated/reported by the lab (Schwarz formula) and used as such in the analysis.

Emergent definition for toxicity grades and abnormalities

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered emergent if it is worse than the baseline abnormality. If the baseline abnormality is missing, the abnormality is always considered as emergent. A shift from "abnormally low" at baseline to "abnormally high" post baseline (or vice versa) is also emergent. The emergence definition is applicable in both, the treatment and follow-up phase.

In case of missing date or partial dates

Laboratory records with missing assessment date- or time-parts (any: day, month or year) will not be used in descriptive statistics, unless the scheduled target day or time is known, and a unique phase allocation is possible taking this additional information into account. These assessments will be allocated to the correct phase using the available date(time) information, and the information on their assessment schedule. In case it is not possible to assign a unique phase (e.g. unscheduled time points), the assessment will be assigned to all possible active phases based on the available date and time information. These cases will be flagged in the respective listings.

Imputations of numerical values expressed as characters

In case a laboratory test result is *censored* (no numeric value is available, but only a verbatim term), the following rules are applied:

- '<x' or '>x': a numeric value will be imputed by a value exceeding the cut-off value with one unit
- '≤x' or '≤x': imputation by x.

This also applies to normal limits expressed as such.

No such imputations will be done for urinalysis parameters as these are usually character/categorical expressions.

Missing normal limits:

Missing normal limits in the database will be imputed at analysis level using the values specified and approved by the sponsor. This only applies if the missing normal limit is critical to determine

a toxicity grade or an abnormality score, i.e. not for tests whose toxicity grade is based on the test value itself. Imputations, if applicable, will be flagged as applicable if shown in listings.

Missing Basophils, Eosinophils, Monocytes, Lymfocytes and Neutrophils values:

There are several methods how basophils, eosinophils, monocytes, lymfocytes and neutrophils (or polymorphonuclear leukocytes PMN) values are reported in the local labs. Some labs provide both the absolute count as well as the percentages as source. However, some sites provide only the one or the other as source. In the latter cases, if only the absolute counts are known, the PMN% will be calculated as follows:

PMN% = (absolute PMN/absolute leukocytes) *100

Vice versa, if only the PMN % are provided, the counts will be calculated as follows:

PMN count = (PMN (%) *WBC count)/ (100)

Reference ranges will not be calculated for derived variables.

6.2.2. Analysis Methods

All lab parameters with numeric values will be analyzed using descriptive statistics on the actual values and changes from baseline over analysis timepoint.

Laboratory toxicity grade, abnormality will be described by frequency and percentage of subjects using below methods:

- Tabulation of the worst-case treatment-emergent toxicity grade and non-graded abnormalities of laboratory parameters per treatment group.
- Cross-tabulations of the worst toxicity grades versus baseline
- Cross-tabulations of the worst laboratory parameter abnormalities versus baseline

Below plots and graphs will be produced to describe the overall and individual evaluations for laboratory parameters by timepoints:

- Individual plot for each laboratory parameter by timepoint.
- Plots of Mean±SE by treatment group over time for actual values and changes from baseline will be generated for all hematology and clinical chemistry tests.

A listing of abnormal individual subject hematology, and clinical chemistry values from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding subject/parameter. Grade 2 or higher toxicity laboratory values will be listed separately. Urinalysis results will be listed.

6.3. Vital Signs and Physical Examination Findings

6.3.1. Definitions

Systolic (SBP) and diastolic blood pressure (DBP), HR, RR, oxygen saturation and body temperature (caregiver or clinical evaluation) will be investigated.

Definitions Grades/Abnormalities

Abnormality codes will be defined as indicated in Table 16. Determining the abnormalities, the following rules are applied:

- Worst grades/abnormalities are determined over the whole evaluation period for each trial phase separately, including post-baseline scheduled and unscheduled measurements of that phase.
- The abnormalities 'abnormally low' and 'abnormally high /grades are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high or graded value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%).

Table 16: Clinically relevant abnormalities – abnormally low/normal/abnormally high

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

Abnormality codes for body temperature are defined as indicated Table 17.

Table 17: 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

if location is missing, we assume 'Rectal.'

In case of missing dates or time parts:

Vital signs records with missing assessment date- or time-parts (any: day, month or year) will not be used in descriptive statistics, unless the scheduled target day or time is known, and a unique phase allocation is possible taking this additional information into account. These assessments will be allocated to the right phase using the available date(time) information, and the information on their assessment schedule. In case it is not possible to assign a unique phase (e.g. unscheduled time points), the assessment will be assigned to all possible active phases based on the available date and time information. These cases will be flagged in the respective listings.

For temperature where each BID assessment defined as morning, afternoon or evening assessment based on the timing of assessment. The following imputation rule will be applied in case of missing time:

- VSTPT is pre-populated and if time is missing and for deriving ARELTM, VSTPT is used to derive timepoint as below
  - Morning – 08:00
  - Afternoon – 16:00
  - Evening – 20:00

Emergence definition for grades/abnormalities

A grade/abnormality will be considered emergent if it is worse than baseline. If baseline is missing, the grade/abnormality is always considered as emergent. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emergent.

6.3.2. Analysis Methods

Incidence of vital signs tests that meet criteria for abnormality will be tabulated for each treatment group.

A cross-tabulation of the worst grade/abnormality versus baseline will be presented for the combination of analysis Treatment and Follow-up phase. This table will also show the number and percentage of subjects per worst grade/abnormality, the number and percentage of subjects per emergent worst grade/abnormality. For Respiratory rate, heart rate and body temperature, the maximum value will be considered as the worst grade/value while for oxygen saturation, the lowest value will be considered the worst one. In determining the maximum body temperature, all temperatures will be considered regardless of whether obtained during on-site visit or measured by caregiver and reported in handheld device.

Mean±SE graphs over time for the actual values and changes from baseline will be generated and presented by treatment group.

A listing of abnormal individual subject vital signs values from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding subject/parameter.

Abnormal physical examination findings will be listed.

6.4. Electrocardiogram

PR, QT, QRS, QTc intervals and heart rate will be investigated. QTcB and QTcF values will be used as reported by the central ECG lab, they will not be recalculated.

6.4.1. Definitions

Definitions Abnormalities

The ECG abnormalities will be defined as indicated in Table 18. ECG abnormalities will be identified based on the subject's age at the time of assessment and as follow:

- Worst grades/abnormalities are determined over the whole evaluation period and for each analysis phase separately, including post-baseline scheduled and unscheduled measurements of that analysis phase.
- The abnormalities 'abnormally low' and 'abnormally high'/grades are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high or graded value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

Table 18: ECG Abnormalities

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	0 - 2 years	NA	>150
QRS (msec)	0 - 2 years	NA	>79
QT/QTc (msec)	0 - 2 years	NA	>500
RR (msec)	0 - 3 months	<333	>750
	3 - 12 months	<400	>860
	1 - 2 years	<430	>1000
Abnormalities on the changes from baseline (ΔQT/QTc)			
	Abnormality Code		**Criteria**
QT/QTc	Borderline QT/QTc change		30 ms < ΔQTc < 60 ms
	Abnormality high QT/QTc change		ΔQTc > 60 ms

Emergent definition for abnormalities

An abnormality will be considered treatment emergent if it is worse than baseline. If baseline is missing, the abnormality is always considered as emergent. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emergent. The emergence definition applies regardless of analysis phase within each analysis phase.

Triplicate ECG assessments

If not available from the central ECG: For time points on which triplicate ECGs apply (expected for all time points), a mean value per triplet cluster, will be calculated per time point before any further handling. This mean value will be used through the entire analysis. In the analysis dataset, the time of the first triplet member will be retained for this average record.

Rounding

When ECG parameters have to be derived or any operations have to be performed (e.g. averaging over many assessments/triplicates), no rounding to the integer/unit will be performed; the maximum stored resolution of these derived values in the derived dataset(s) will be limited to 8 decimal positions. When used in tables, these values will be presented using formats reflecting the resolution of the unit applicable to the respective parameter (milliseconds, beats per minute).

6.4.2. Analysis Methods

Incidence of ECG parameters that meet criteria for abnormality will be tabulated for each treatment group.

A cross-tabulation of the worst abnormality versus baseline will be presented for the combination of analysis Treatment and follow-up phase. This table will also show the number and percentage of subjects per worst toxicity/abnormality, the number and percentage of subjects per emergent worst toxicity/abnormality.

A tabulation of the worst QT/QTc change versus baseline per for the combination of analysis treatment and follow-up phase will be presented.

Tabulation of participants per QT/QTc category for actual values (]450ms,480ms],]480ms,500ms] and more than 500ms) and category for change from baseline (<=30, >30-60, >60) will be presented. This table will show the number and percentage of participants in each category

Mean±SE graphs over time for the actual values and changes from baseline will be generated and presented by treatment group.

A listing of abnormal individual subject ECG values from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding subject/parameter.

7. VIROLOGY

7.1. 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 subjects 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 subjects (if viral load is high enough) to identify emerging amino acid substitutions in the 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 subject'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, i.e. with an NGS read frequency <3%, at baseline but detected with an 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 an 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:
  - 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

Virology results will be assigned to the visit windows as described in Sections 2.1.1 and 2.1.4. In addition to the time points corresponding 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.
- Any post-baseline time point in the study with sequencing data available.

7.2. Analysis Methods

7.2.1. Viral Sequencing

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 subjects 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 subjects using a NGS read frequency cut-off of 3%. For subjects with emerging or enriched genetic variations, RSV RNA viral load profiles including emerging or enriched genetic variations per time point, will be generated.

8. OBSERVATIONAL STAGE

This section covers analyses related to the observational stage only.

All rules, definitions, and imputations described for the interventional stage also apply on the observational stage data unless otherwise described in this section. Rules and definitions of the RSV (+) non-interventional subjects are similar to the interventional stage subjects to ensure that results can be compared with results from the interventional stage.

8.1. General Analysis Definitions

8.1.1. Visit Windows and Phase Definitions

Phase Definitions

Phases will be constructed as defined in Table 19 below:

Table 19: Analysis phases for subjects in observational stage

Analysis Phase [number]	Start Date/Time	End Date/Time	Subjects to which Phase Applies
Observational Screening [1]	00:00 of the date of signing the informed consent form for the observational stage	23:59 of the date of signing the informed consent form for the observational stage	All subjects enrolled in the observational stage
Observational Pre-diagnosis [2]	1 minute after the End of the Screening Phase	Date and time of the RSV (+) diagnostic test result or trial termination	All subjects enrolled in the observational stage
Observational Post-diagnosis [3]	1 minute after the End of Pre-diagnosis Phase	23:59 of the day of trial termination (date of last contact)	RSV (+) subjects not enrolled in the interventional stage

Thus a subject without ARI visits and/or with only RSV (-) diagnostic test result(s) will remain in the Pre-diagnosis Phase until the study ends.

Assessments will be assigned to phases based on their datetime, 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. 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.

Baseline

In the observational stage, only the RSV (+) subjects will be assigned a baseline record. The baseline record is defined as the first record on the day of the RSV (+) ARI visit. If this is not available, the first available record after the day of the RSV (+) ARI visit is considered baseline.

Relative Day

In the observational stage, two relative day variables are defined. All assessments at all visits will be assigned a day relative to these dates.

- The first relative day variable starts counting from the ICF date (RD_{obs}) and Day 1 is defined as the date of signing the informed consent form for the observational stage.
- The second relative day item (RD_{diag}) starts counting from the RSV (+) ARI visit and Day 1 is defined as the date of the RSV(+) ARI visit.

The relative day will be defined as:

$$reldy = visit\ date - reference\ date + 1$$

for visits on or after Day 1, and

$$reldy = visit\ date - reference\ date$$

for visits before Day 1. There is no 'Day 0'.

Analysis Windows for Analysis Visits and Time Points

For the RSV (+) subjects, the visit windows and the target days are defined for each visit of the protocol using the definition defined for the interventional stage in Section 2.1.4. The same visit window mapping is applied to ensure that results of the RSV (+) observational subjects can be compared with results from subjects of the interventional stage. Similar rules as in the interventional stage will be applied to have only one evaluation per subject per analysis visit.

Please note the following differences in the visit schedule and assessments in the observational stage as compared to the interventional stage for the RSV (+) subjects:

- Mid-turbinate nasal swabs from Day 1 to Day 8 only.
- For RSV (+) outpatients clinician evaluation and clinician PRESORS available on Day 1 only.
- No temperature logs are being completed
- No safety assessments (blood pressure, directed physical examination, ECG) performed (for RSV (+) subjects who did not enroll in the interventional stage and stay in observational stage)

For the RSV Mobile App questionnaire, the morning and evening time point is defined as:

Slot of the Day	Time	Target
Morning	00:00 – 19:59	08:00
Evening	20:00 – 23:59	20:00

Note: these time-windows are defined based on the time when the RSV Mobile App pushes the questionnaires to the parents/caregivers of the participants. The Morning questionnaires is pushed at 08h00 and parents/caregivers have time until 19h59 to complete it. The Evening questionnaire is pushed at 20h00 and is available until 23h59.

8.1.2. Analysis Sets

The following analysis sets are defined for the observational stage:

- **All Enrolled Analysis Set – Observational Stage**: All participants who signed the ICF of the observational stage and were classified as eligible.
- **ARI-Visit Analysis Set – Observational Stage**: All the subjects who completed at least one study related ARI visit with RSV diagnostic test result available.
- **RSV (+) Analysis Set – Observational Stage**: All the subjects with a positive RSV diagnostic test who did not enter the interventional stage.
- **RSV (+) Analysis Set – Overall**: All the subjects with a positive RSV diagnostic test result in the study (includes both RSV (+) interventional and observational stage subjects).

For the observational stage the *Safety Analysis Set* is the same as the All-Enrolled Analysis Set.

When referring in the text below to 'observational stage analysis sets' this indicates the first 3 analysis sets defined above: All Enrolled Analysis Set – Observational Stage; ARI-Visit Analysis Set – Observational Stage; RSV (+) Analysis Set – Observational Stage.

8.1.3. Definition of Subgroups

The subgroups defined for the observational stage are similar as those defined in the interventional stage. Subgroup analyses is performed for selected viral load outputs. Other subgroup analyses could be performed post-hoc if it is deemed useful to be combined with the interventional stage.

Table 20: Subgroup definitions

Subgroup	Subjects to which it applies	Definition
Symptom Onset before ARI Visit	Subjects in RSV(+) Analysis Set – Observational stage	• Subjects with symptom onset ≤3 days before ARI Visit • Subjects with symptom onset >3 days before ARI Visit
RSV Subtype	Subjects in RSV(+) Analysis Set – Observational stage	• RSV A • RSV B • RSV A+B

8.2. Subject Information

8.2.1. Demographic and Subject Characteristics

Table 21 presents demographics at observational stage enrollment that will be summarized descriptively for the *observational stage analysis sets* and the *RSV (+) Analysis Set – Overall*. Table 22 presents subject characteristics at enrollment that will be summarized descriptively for the *observational stage analysis set*s and the *RSV (+) Analysis Set – Overall*.

Table 21: Demographics at Observational Stage Enrollment

Continuous Variables	**Summary Type**
Age at enrollment (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight at birth (kg)	
Length/Height at birth (cm)	
Categorical Variables	
Sex (male, female, unknown, undifferentiated)	Counts (n, %)
Age Group at enrollment (< 14 days; ≥14 days and <30 days; ≥30 days and <60 days, ≥60 days and ≤4 months)	
Ethnicity[a] (Hispanic or Latino, Not Hispanic or Latino, Not Reported)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not Reported)	
Country	

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

Table 22: Subject Characteristics at Observational Stage Enrollment

Continuous Variables	**Summary Type**
Gestational age, if ≥ 37 weeks (weeks)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Number of other siblings within the household	
Categorical Variables	
Prematurely born (i.e. <37 weeks gestational age) (no, yes)	Counts (n, %)
Prenatal Smoking by the subject's mother (no, yes)	
Exposed to tobacco smoke in home environment (no, yes)	
Other siblings in household (no, yes)	
Contact with other children (siblings, kindergarten, daycare) (no, yes)	
History of atopy/allergy (no, yes)	
Feeding type (only breast milk; only formula; combination of breast milk and formula; solid food only; solid food combined with milk/formula)	
Breastfeeding ongoing (no, yes)	
Currently attending daycare (no, yes) If yes, days per week (1, 2, 3, 4, 5, 6, 7) If no, will child attend day care in the future (yes, no)	
Received Palivizumab (no, yes)	
Mode of delivery (vaginal, C-section, not documented)	

Table 23 presents caregiver information at enrollment (collected in the eCRF) that will be summarized descriptively for the *observational stage analysis set*s and the *RSV (+) Analysis Set – Overall*.

Table 23: Caregiver Information at Observational Stage Enrollment

Categorical Variables	**Summary Type**
Educational level of mother (Did not Complete Secondary School or Less than High School; Some Secondary or High School Education; High School or Secondary School Degree Complete; Associate's or Technical Degree Complete; College or Baccalaureate Degree Complete; Doctoral or Post Graduate Education: More than High School; I do not wish to answer; Unknown; Not Applicable)	Counts (n, %)
Educational level of father (Did not Complete Secondary School or Less than High School; Some Secondary or High School Education; High School or Secondary School Degree Complete; Associate's or Technical Degree Complete; College or Baccalaureate Degree Complete; Doctoral or Post Graduate Education: More than High School; I do not wish to answer; Unknown; Not Applicable)	
Educational level of caregiver (Did not Complete Secondary School or Less than High School; Some Secondary or High School Education; High School or Secondary School Degree Complete; Associate's or Technical Degree Complete; College or Baccalaureate Degree Complete; Doctoral or Post Graduate Education: More than High School; I do not wish to answer; Unknown; Not Applicable)	
Occupational/employment status mother (Full Time Employed; Part Time Employed; Unemployed; I do not wish to answer; Not Applicable)	
Occupational/employment status father (Full Time Employed; Part Time Employed; Unemployed; I do not wish to answer; Not Applicable)	
Occupational/employment status caregiver (Full Time Employed; Part Time Employed; Unemployed; I do not wish to answer; Not Applicable)	

Table 24 and Table 25 present demographic and baseline characteristics for the observational RSV(+) subjects as observed during the RSV(+) ARI Visit. This information will be summarized descriptively for the *observational stage analysis sets* and the *RSV (+) Analysis Set – Overall*.

Table 24: Demographics at ARI Visit for Observational Stage RSV (+) Subjects

Continuous Variables	**Summary Type**
Age at ARI visit (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight at ARI visit (kg)	
Length/Height at ARI visit (cm)	
Head Circumference at ARI visit (cm)	
Categorical Variables	
Age Group (≥28 days and <3 months, ≥3 months and <6 months, ≥6 months)	Counts (n, %)
Setting (Hospitalized, Outpatient)	

Table 25: Characteristics at ARI Visit for Observational Stage RSV (+) Subjects

Continuous Variables	**Summary Type**
Duration of RSV symptoms prior to ARI visit (days)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
RSV Viral Load (log_{10} copies/ml)*	
RSV Viral Load (log_{10} copies/ml)* by RSV Subtype	
RSV Viral Load (log_{10} copies/ml)* by symptom onset	
Respiratory Rate (breaths/min)	
Heart Rate (beats/min)	
Oxygen Saturation (%)	
Categorical Variables	
RSV Subtype (RSV A, RSV B, RSV A+B)	Counts (n, %)
Symptom onset (≤3 days, >3 days) prior to ARI visit	
Presence of risk factors for severe RSV disease (no, yes)	
Received palivizumab (no, yes)	
Received aerosolized ribavirin (no, yes)	
Received IV immunoglobulin (no, yes)	

*Only nasal mid-turbinate swab type samples to be considered.

8.2.2. Disposition Information

Summaries will be provided for the following disposition information:

- Number of subjects screened
- Number of subjects in respective analysis sets
- Number of RSV (+) subjects in study
  - Enrollment in interventional stage
  - Not enrolled in interventional stage
- Enrollment by country and site
- Number of subjects who completed or discontinued the observational stage of the trial, with a breakdown of the reasons for discontinuation.

8.2.3. Protocol Deviations

All major protocol deviations related to the observational stage will be listed.

8.2.4. Medical History and Family History

The medical history and family history records will be listed for the *RSV (+) Analysis Set – Observational Stage*.

8.3. Adverse Events

All reported adverse events related to the observational stage will be listed.

8.4. Observational Stage Endpoints and Analysis

The analyses include the endpoints related to the observational stage. Definitions of the endpoints are similar as in the interventional stage, unless otherwise described here. Analyses of blood, buccal swab and stool microbiome samples are out of scope of this Statistical Analysis Plan.

The endpoints applied to the observational stage:

- the total score, over time, of respiratory symptoms as captured by the RSV mobile App during the pre-diagnostic phase and the post-diagnostic phase for RSV(+) participants who do not enter in the interventional stage
- the PRESORS scores by the clinician (clinician PRESORS) on the day of RSV diagnosis for RSV(+) participants who do not enter in the interventional stage
- RSV viral load kinetics during the pre-diagnostic phase
- RSV viral load kinetics from Day 1 to Day 8 after RSV diagnosis over time for RSV(+) participants who do not enter in the interventional stage
- the PRESORS scores by parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) over time for RSV(+) participants who do not enter in the interventional stage

The endpoints applied to the exploratory objectives of the observational stage are:

- the frequency and severity of individual symptoms based on the RSV mobile App, over time
- the frequency and severity of clinician recorded symptoms based on the PRESORS (clinician PRESORS) on the day of RSV diagnosis for RSV(+) participants who do not enter in the interventional stage
- the individual signs and symptoms and total score that triggered ARI visit
- participation in the interventional stage
- correspondence of disease characteristics as assessed by the investigator at the site (ClinRO PRESORS) and scores as assessed by parent(s)/caregiver(s) (ObsRO PRESORS and RSV Mobile App)
- characteristics of parent(s)/caregiver(s) (optional) and infant at baseline in relation to (but not limited to) RSV mobile App compliance, protocol adherence, and enrollment in interventional stage

8.4.1. Hypothesis

For the observational stage, no formal hypothesis will be tested.

8.4.2. RSV Mobile App Related Endpoints and Analysis

8.4.2.1. RSV Mobile App Questions, Answers and Scoring Endpoints

Definitions:

In the RSV Mobile App there are several symptom/sign questionnaires that the parents should complete depending on the RSV-status of their child.

- *Pre-diagnosis* questionnaire: This is the main questionnaire that all parent(s) need to complete. It monitors the child's symptoms and has an associated algorithm to calculate the disease severity based on a scoring. This questionnaire is active every day, once in the morning and once in the evening (until a child is diagnosed RSV(+)).
- *Trigger button* questionnaire: During the pre-diagnosis phase, a parent/caregiver can decide to self-report besides the two *pre-diagnosis* questionnaires per day. In such a case, the parents receive exactly the same questionnaire as the *pre-diagnosis* questionnaire.
- Hospitalization questionnaire: This questionnaire is active during the hospital stay of a RSV(+) subject.
- *Outpatient* questionnaire: This questionnaire should be completed only for RSV(+) subjects in the outpatient setting (including the subjects who are discharged from the hospital setting).

The type of questionnaires is captured in the database as it is provided by the RSV Mobile App vendor.

The following endpoints are defined:

- Individual questions and answers on the RSV Mobile App questionnaire during *pre-diagnosis* and *trigger button*:

Question	Question name	Possible Answers
Does the baby have a runny or stuffy nose?	RUNSTUF	• No • Yes
What is the color of the mucus?	COLOR	• Clear mucus, no color • White mucus • Yellow or green mucus • No mucus, just stuffy nose
Does the baby have a cough?	COUGH	• No • Yes
How often does the baby cough during a period of 5 minutes?	COUGHFR5	• Less than once (individual coughs) • Between 1 and 10 times (continuous coughing) • More than 10 times (or more than twice per minute) (bouts of coughing)
What is the strength of the coughing?	COUGHST	• Weak • Strong • Very strong, causing sometimes vomiting or interference with feeding and sleeping
Does the baby show problems breathing?	BABYPRBR	• No • Yes

Did your child pause breathing for more than 10 seconds?	BREAT10S	• No • Yes
How many breaths does the baby take in 30 seconds (Please count)?	BREAT30S	Continuous parameter
Do the baby's nostrils flare out when breathing?	FLARE	• No • Yes
While breathing, does the baby's belly pull in and/or does the skin pull in below the neck?	SKINPULL	• No • Yes
Does the baby make noise while breathing?	NOISEBR	• No • Yes
What kind of noise does the baby make when breathing?	NOISEMK	• None of the below • Whistling / wheezing • Chesty sound • Grunting sound
Does the baby show any of following signs of not feeling well?	SGNFEEL	• Less activity • Tired more easily • Less interested in playing with toys • Clinging to you or had to be held or carried • Not responding to you as usual
How much did the baby eat in the last 8 hrs?	EATING8H	• As normal • Did not complete 1 of his/her regular feedings • Did not complete more of his/her regular feedings (+2) • Did not eat at all
Did the baby vomit in the last 8 hrs?	VMT8H	• No • Did vomit once or twice • Did vomit more than twice
Is the baby crying more than usual?	BABYCRY	• No • Yes, more than usual • Yes, a lot more than usual
How easy was the baby calmed when held or soothed?	CALMEASY	• baby calmed easily • baby was difficult to calm • baby did not calm
How would you assess the color of your baby's skin?	SKNCLR	• Normal • Paler than usual
Did the baby have fever?	FEVER	• No • Yes
Did the baby receive medication to lower the fever?	FEVERMD	• No • Yes • Don't know
Did the baby have a wet diaper in the last 8hrs?	WET8H	• Yes • No • Don't know

- Individual questions and answers on the RSV Mobile App *hospitalization* questionnaire:

  RUNSTUF, COLOR, COUGH, COUGHFR5, COUGHST, NOISEBR, NOISEMK, SGNFEEL, EATING8H, VMT8H, BABYCRY, CALMEASY,

WET8H

- Individual questions and answers on the RSV Mobile App *outpatient* questionnaire:

  RUNSTUF, COLOR, COUGH, COUGHFR5, COUGHST, BREAT10S, BREAT30S, NOISEBR, NOISEMK, SGNFEEL, EATING8H, VMT8H, BABYCRY, CALMEASY, SKNCLR, FEVER, FEVERMD, WET8H

- Symptom summary scores, domain scores (respiratory signs scores; non-respiratory signs score) and total score on the RSV Mobile App questionnaire as described in Attachment 4.

Analysis Methods:

- Individual question and answers on the RSV Mobile App questions:
  - Te proportion of answers within the categories by question will be shown in a frequency tabulation, as well as graphically by barplots [by pre-diagnosis, trigger button, hospitalization and outpatient questionnaires]
- Symptom summary scores:
  - For the questionnaires that triggered an ARI visit (ARI alerts), the proportion of answers within the categories by each symptom summary score will be shown in a frequency tabulation, as well as graphically by barplots
- Respiratory signs scores, non-respiratory signs score and total score on the RSV Mobile App:
  - Graphical representation (mean, SE) of the RSV Mobile App respiratory signs score, non-respiratory signs scores and total score over time before ARI alert [during pre-diagnosis stage, 0 to 10 days before ARI alert]. Different colors will be used for RSV (+) and RSV(-) subjects. ARI alerts that did not lead to an RSV diagnostic test result are not included in this analysis.
- Graphical representation (mean, SE) of the RSV Mobile App respiratory signs scores, non-respiratory signs score and total score over time (Day 1 to 21) after RSV(+) diagnosis.
- A summary of the total score during the pre-diagnosis stage will be shown in a tabulation:
  - Number of completed questionnaires
  - Number of completed questionnaires with total score = 0
  - Number of completed questionnaires with total score > 0, and the distribution of each possible score

8.4.2.2. Definitions of RSV Mobile App and ARI Visit Endpoints

Definitions:

The following endpoint is defined:

- Time (in hours) between RSV Mobile App alert and RSV diagnostic test at ARI visit: Endpoint = Date/time RSV-diagnostic test – Date/time of ARI alert (in hours)

  In case no ARI visit / RSV-diagnostic test was performed or in case the date and/or time of the RSV-diagnostic test is not available, this endpoint will be missing.

Analysis Methods:

- Time (in hours) between RSV Mobile App alert and RSV diagnostic test at ARI visit:
  - Number of ARI alerts (N, and unique subjects)
  - Number of ARI visits (N, and unique subjects)
  - Number of RSV-diagnostic tests with date/time (N, and unique subjects)
    - Descriptive statistics (N, mean, standard deviation [SD], median, IQR and range [minimum and maximum])
    - Categorical: <12 hours; 12 -< 24 hours; 24 -< 48 hours; >=48 hours
    - Graphical representation by histogram [by site]

8.4.2.3. Definitions of RSV Mobile App Compliance Endpoints

Definitions and Analysis methods:

The following information will be summarized with respect to the completion of the RSV Mobile App questionnaires:

Table 26: RSV Mobile App Compliance

Continuous Variables	**Summary Type**
Number of completed RSV Mobile App questionnaires by subject [overall; by questionnaire type (pre-diagnosis, hospitalization, outpatient, trigger button)]	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Completion rates of RSV Mobile App questionnaire (planned/completed*100) by subject [overall; by timepoints and questionnaire type (pre-diagnosis, hospitalization, outpatient)]	
Categorical Variables	
Number of subjects with completed RSV Mobile App questionnaires [overall; by questionnaire type (pre-diagnosis, hospitalization, outpatient, trigger button)]	Counts (n, %)
Number of RSV Mobile App questionnaires planned & completed [overall; by timepoint and questionnaire type (pre-diagnosis, hospitalization, outpatient)]	

- Graphical representation of the RSV Mobile App compliance over time by plotting the number of completed RSV Mobile App questionnaires and completion rates [by timepoint; by country and timepoint].

The following information will be summarized with respect to the RSV Mobile App Alerts:

Table 27: RSV Mobile App Alerts

Continuous Variables:	**Summary Type**
Number of RSV Mobile App Alerts by subject	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Categorical Variables	
Total number of RSV Mobile App Alerts	n
Total number of unique subjects with at least one RSV Mobile App Alert	n, %
Number of RSV Mobile App Alerts per subject: • Number of subjects with 1 RSV Mobile App alert • Number of subjects with 2 RSV Mobile App alert • Etc.	n, %
RSV Mobile App Alert and ARI visit: • ARI visit was not performed • ARI visit took place	n, %

8.4.2.4. Definitions of RSV Mobile App and Nasal Swab at Home Endpoints

Definitions and Analysis methods:

The following information will be tabulated:

- Number of RSV Mobile App Alerts
- Number of missing nasal swabs at home at ARI alerts
- Number of available nasal swabs at home at ARI alerts

8.4.3. PRESORS Related Endpoints and Analysis

The ObsRO and ClinRO PRESORS scoring system is similar as defined in the interventional stage.

All the time-to variables are calculated using the start date/time set equal at the date/time of the RSV (+) diagnostic test result.

Definitions ObsRO PRESORS Endpoints:

The following defined ObsRO endpoints are considered:

- ObsRO concept scores + change from baseline
- ObsRO summary scores + change from baseline
- Daily summary scores
- Time to resolution of all RSV symptoms (hours) [Time-to event]
- Time to resolution of key RSV symptoms (hours) [Time-to event]
- Time to resolution of respiratory symptoms (hours) [Time-to event]

- Time to resolution of general illness behavior symptoms (hours) [Time-to event]
- Status of RSV symptoms at each time point (general question) [categorical]
- Status of health at each time point (general question) [categorical]
- Status of improvement of RSV symptoms at each time point (general question) [categorical]
- Time to improvement of RSV symptoms (general question) [Time-to event]
- Status of return to pre-RSV disease health at each time point [categorical]

Definitions ClinRO PRESORS Endpoints on the Day of RSV Diagnosis:

The following defined ClinRO endpoints are considered:

- ClinRO concept scores
- ClinRO summary scores
- Status of overall condition [categorical]
- Status of health [categorical]

Definitions ClinRO PRESORS Endpoints for the RSV (+) Hospitalized Subjects:

The following analysis is performed in case at least 10 RSV (+) subjects are being hospitalized in the observational stage.

The following defined ClinRO endpoints are considered:

- ClinRO concept scores + change from baseline
- ClinRO summary scores + change from baseline
- ClinRO daily summary scores
- Status of overall condition at each time point [categorical]
- Status of health at each time point [categorical]
- Health compared to the baseline assessment [categorical]

Analysis Methods:

- ObsRO concept, summary and daily scores; ClinRO concept, summary and daily scores:
  - Descriptive statistics and mean (SE) graphs will be shown for the actual values and changes from baseline by visit. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 90% confidence interval, median, range and interquartile range. Descriptive statistics will be presented overall.

- Time-to-event variables:
  - Time-to event variables will be analyzed using Kaplan-Meier analysis. The 90% 2-sided confidence intervals will be presented.
- Categorical variables:
  - The proportion of subjects within the categories will be shown in a frequency tabulation, as well as graphically, per analysis time point (with corresponding 90% CIs) and visit. Subjects with missing data on that analysis visit will not be counted in the denominator for the proportion.

8.4.4. RSV Viral Load Kinetics Endpoints and Analysis

Similar data handling rules for the RSV viral load, as described in Section 5.2.2, for the interventional stage are applied for the observational stage.

Definitions RSV viral load kinetics during the pre-diagnostic phase:

The following defined RSV viral load endpoints are:

- RSV Viral load categorization of samples collected during the pre-diagnostic phase at home (can include both RSV(-) and RSV(+)) [categorical: Undetectable; Detectable; Quantifiable]
- Log_{10} RSV viral load actual values of the RSV(+) samples (those with detectable or quantifiable RSV viral load) collected during the pre-diagnostic phase at home

Definitions RSV viral load kinetics from Day 1 to Day 8 for RSV(+) subjects:

The following defined RSV viral load endpoints are considered:

- Log_{10} RSV viral load actual values
- Log_{10} RSV viral load change from baseline
- RSV Viral load status at each time point [categorical: Undetectable; Detectable; Quantifiable]
- Time to virus undetectable (hours) [time-to-event]

Analysis Methods:

- Categorical variable:
  - The proportion of subjects within the RSV viral load categories (undetectable, detectable and quantifiable) will be shown in a frequency tabulation, as well as graphically by visit. Subjects 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 RSV viral loads denote worse degree of infection, the ordering will be from worst to better namely: quantifiable; detectable; undetectable.
- Log_{10} RSV viral load:
  - Descriptive statistics and mean (SE) graphs will be shown for the log_{10} RSV viral load actual values and changes from baseline by visit from Day 1 to Day 8. Descriptive

statistics will include the number of subjects, mean, standard deviation, standard error, 90% confidence interval, median, range and interquartile range. Descriptive statistics will be presented for the log_{10} RSV viral load actual values of the RSV(+) samples collected during the pre-diagnostic phase at home.

  - Descriptive statistics and mean (SE) graphs will be shown for the log_{10} RSV viral load actual values and changes from baseline by visit from Day 1 to Day 8 by RSV subtype.

- Time to virus undetectable:
  - This time-to event variable will be analyzed using Kaplan-Meier analysis. A summary table including number of subjects included in the analysis, number of subjects censored, 25^{th} and 75^{th} percentiles and median time-to event, with confidence intervals based on log-log transformation method will be presented. The data will be presented graphically using the Kaplan-Meier estimate of the survival function.

8.4.5. RSV(+) Hospitalized Endpoints and Analysis

The following analysis is performed in case at least 10 RSV(+) subjects are being hospitalized in the observational stage.

Definitions vital signs endpoints:

The following defined endpoints are considered:

- Respiratory Rate (RR) actual values + changes from baseline
- Heart Rate (HR) actual values + changes from baseline
- Oxygen Saturation (SpO2) actual values + changes from baseline
- Body Temperature (clinician) actual values + changes from baseline

Analysis Methods:

- Viral sign variables:
  - Descriptive statistics and mean (SE) graphs will be shown for the actual values and changes from baseline by visit. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 90% confidence interval, median, range and interquartile range.

8.4.6. Correspondence of Disease Characteristic Endpoints and Analysis

Definitions:

The following RSV disease characteristics scores are considered for the investigator:

- PRESORS ClinRO daily summary scores

The following RSV disease characteristics scores are considered for the parent/caregiver:

- PRESORS ObsRO daily summary scores
- RSV **Mobile** App respiratory signs score, non-respiratory signs scores and total score

Analysis Methods:

The following analysis is performed for all RSV(+) subjects in the observational stage:

- Scatterplot of the ClinRO daily summary scores vs the ObsRO daily summary scores on the day of the ARI visit. Spearman correlation will be added to the scatterplot.
- Scatterplot of the ClinRO daily summary scores vs the RSV Mobile App scores on the day of the ARI visit. Spearman correlation will be added to the scatterplot. (in case multiple RSV Mobile App scores are available on that day, the maximum value is used in the scatterplot).
- Scatterplot of the ObsRO daily summary scores vs the RSV Mobile App scores on the day of the ARI visit. Spearman correlation will be added to the scatterplot. (in case multiple RSV Mobile App scores are available on that day, the maximum value is used in the scatterplot).
- Scatterplot of the ObsRO daily summary scores vs the RSV Mobile App scores from Day 1 to Day 21. Spearman correlation will be added to the scatterplot. (in case multiple RSV Mobile App scores are available on that day, the maximum value is used in the scatterplot).

The following analysis is performed for all hospitalized RSV(+) subjects in the observational stage on the days with at least 10 subjects available:

- Scatterplot of the ClinRO daily summary scores vs the ObsRO daily summary score on each day (Day 1 to Day 21). Spearman correlation will be added to the scatterplot.
- Scatterplot of the ClinRO daily summary scores vs the RSV Mobile App scores on each day (Day 1 to Day 21). Spearman correlation will be added to the scatterplot. (in case multiple RSV Mobile App scores are available on that day, the maximum value is used in the scatterplot).

8.4.7. Interventional Stage Participation Endpoints and Analysis

Definitions:

- The following binary endpoint is created for all study enrolled subjects with a RSV(+) diagnostic test [RSV(+) Analysis Set – Overall]:
  - Enrolled in interventional stage (Yes, No)

Analysis methods:

Demographic, enrollment characteristics and ARI-visit characteristics split by this binary endpoint are presented in Tables 19 - 23. The following information will further be tabulated for the RSV Mobile App Scores by the binary endpoint and overall:

Table 28: Interventional Stage Participation Characteristics

RSV Mobile App	
Respiratory summary scores	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Non-respiratory summary score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Total score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).

8.4.8. Parent/Caregiver and Child Characteristics Endpoints and Analysis

Definitions:

- The following endpoints are created for all study enrolled subjects:
  - RSV Mobile App questionnaire compliance (completed/planned * 100 %): [< 25%; 25 - < 50%; 50 - <75%; ≥75%]. Trigger button RSV Mobile App questionnaires are not considered.
  - Protocol adherence: [Yes: no major protocol deviations associated with parent/caregiver of subject; No: at least one major protocol deviations associated with parent/caregiver of subject]
    - Note: defining major protocol deviations associated with parent/caregiver of subject is performed after database lock based on information provided in Deviation domain.

Analysis methods:

Table 29 presents caregiver information at enrollment that will be summarized for the following endpoints by category and overall:

- RSV Mobile App Compliance
- Protocol adherence

Table 29: Child and Parent/Caregiver characteristics for RSV Mobile App Compliance, Protocol adherence and Enrolled in interventional stage

Categorical Variables:	Summary Type
Educational level of mother (Did not Complete Secondary School or Less than High School; Some Secondary or High School Education; High School or Secondary School Degree Complete; Associate's or Technical Degree Complete; College or Baccalaureate Degree Complete; Doctoral or Post Graduate Education: More than High School; I do not wish to answer; Unknown; Not Applicable)	Counts (n, %)
Educational level of father (Did not Complete Secondary School or Less than High School; Some Secondary or High School Education; High School or Secondary School Degree Complete; Associate's or Technical Degree Complete; College or Baccalaureate Degree Complete; Doctoral or Post Graduate Education: More than High School; I do not wish to answer; Unknown; Not Applicable)	
Educational level of caregiver (Did not Complete Secondary School or Less than High School; Some Secondary or High School Education; High School or Secondary	

Table 29: Child and Parent/Caregiver characteristics for RSV Mobile App Compliance, Protocol adherence and Enrolled in interventional stage

Categorical Variables:	Summary Type
School Degree Complete; Associate's or Technical Degree Complete; College or Baccalaureate Degree Complete; Doctoral or Post Graduate Education: More than High School; I do not wish to answer; Unknown; Not Applicable)	
Occupational/employment status mother (Full Time Employed; Part Time Employed; Unemployed; I do not wish to answer; Not Applicable)	
Occupational/employment status father (Full Time Employed; Part Time Employed; Unemployed; I do not wish to answer; Not Applicable)	
Occupational/employment status caregiver (Full Time Employed; Part Time Employed; Unemployed; I do not wish to answer; Not Applicable)	
Country	
Age subject at enrollment (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Age Group at enrollment (< 14 days, ≥14 days and <30 days, ≥30 days and <60 days, ≥60 days and ≤4 months)	Counts (n, %)
Number of siblings within the household	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Prenatal Smoking by the subject's mother (no, yes)	Counts (n, %)
Exposed to tobacco smoke in home environment (no, yes)	
Routinely attending daycare (no, yes)	
Other siblings in household (no, yes)	

8.4.9. Additional Analysis

The following analysis are performed:

- Summary of the RSV Mobile App evaluation questions. The proportion of subjects within the categories of each question will be shown in a frequency tabulation.
- Scatterplot of the log10 RSV viral load values vs the RSV Mobile App domain scores on the day of the ARI visit. Spearman correlation will be added to the scatterplot.
- Scatterplot of the log10 RSV viral load values vs the ClinRO summary score on the day of the ARI visit. Spearman correlation will be added to the scatterplot.
- Scatterplot of the log10 RSV viral load values vs the ObsRO daily summary score on the day of the ARI visit. Spearman correlation will be added to the scatterplot.
- Cumulative distribution of enrollment in the study (observational stage) over time, overlaid with the cumulative distribution of the ARI alerts over time.
- Frequency tabulation of each individual RSV Mobile App question at ARI alert (using the symptom summary scores) by RSV +/- diagnosis. ARI alerts without diagnosis are not considered. For example, for "What is the strength of the coughing?"

	RSV(-) N=	RSV(+) N=
Weak	n xx.x %	n xx.x %
Strong	n xx.x %	n xx.x %
Very strong, causing sometimes vomiting or interference with feeding and sleeping	n xx.x %	n xx.x %

8.4.10. Subject Profiles

Individual profiles of the $\log_{10}$ RSV viral load actual values will be created for each RSV(+) subject in the observational stage. Values from samples collected during the pre-diagnostic phase at home and collected during Day 1 to Day 8 are used.

Individual profiles of respiratory signs scores, non-respiratory signs score and total score on the RSV Mobile App will be created for each RSV(+) subject in the observational stage. RSV App Scores will be presented from Day -10 to Day 21 of the ARI visit.

Individual profiles combining the $\log_{10}$ RSV viral load actual values and the RSV App total scores will be created for each RSV(+) subject in the observational stage.

Individual profiles combining the daily ObsRO summary scores and the RSV App total scores will be created for each RSV(+) subject in the observational stage.

REFERENCES

1. Ruvuna F., Flores D, Mikrut B., De La Garza K, Fong S. Generalized Lab Norms for Standardizing Data from Multiple Laboratories. Drug Information Journal 2003; 37: 61-79

2. Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. J Am Soc Nephrol. 2009; Nov; 4(11): 1832-643.

ATTACHMENTS

Attachment 1: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007; draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

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

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

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

SERIOUS OR LIFE-THREATENING ADVERSE EVENTS

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

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria [CTC], and WHO) have been adapted for use by the DMID and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following toxicity tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.

- Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

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

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

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

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

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

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

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

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

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 - 1.75 x ULN	>1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
Pancreatic Amylase	1.1 - 1.4 x ULN	1.5 - 1.9 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
Uric Acid	7.5 - 9.9 mg/dL	10 - 12.4 mg/dL	12.5 - 15.0 mg/dL	>15.0 mg/dL
CPK	See Neuromuscular Toxicity			
Appetite	-	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal Pain	Mild	Moderate- No Treatment Needed	Moderate- Treatment Needed	Severe- Hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

ELECTROLYTES (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypernatremia	-	<145 - 149 mEq/L	150 - 155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia	-	130 - 135 mEq/L	129 - 124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0 - 5.9 mEq/L	6.0 - 6.4 mEq/L	6.5 - 7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0 – 3.5 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5 - 11.2mg/dL	11.3 - 11.9 mg/dL	12.0 - 12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.0 - 6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2 - 1.4 mEq/L	0.9 - 1.1 mEq/L	0.6 - 0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55 - 65 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116 - 159 mg/dL	160 - 249 mg/dL	250 - 400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150-499 mg/day	3+ or 500-1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf	-	Gross hematuria

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

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

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007
(Older than 3 months of age)

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

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