Janssen Research & Development *

Statistical Analysis Plan

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of Orally Administered Lumicitabine (JNJ-64041575) Regimens in Hospitalized Infants and Children Aged 28 Days to 36 Months Infected with Respiratory Syncytial Virus

Protocol 64041575RSV2004; Phase 2

Lumicitabine (JNJ-64041575, ALS-008176)

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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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AMENDMENT HISTORY

Not applicable

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AUC	area under the plasma concentration-versus time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-versus time curve from time 0 to 24 hours after dosing
$AUC_{0\text{-}last}$	are under the plasma curve from time 0 to the time of the last quantifiable concentration
C_{12h}	predicted concentration at 12 hours post dose
C_{max}	maximum observed (or predicted) analyte concentration
CV	Coefficient of variation
DBP	diastolic blood pressure
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
HCP	Health Care Provider
ICF	informed consent form
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
ITT	intent-to-treat
ITT-i	intent-to-treat infected
IV	intravenous
IWRS	interactive web response system
LD	loading dose
LRTI	lower respiratory tract infection
MD	maintenance dose
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
popPK	population-derived pharmacokinetic(s)
PRESORS	Pediatric RSV Electronic Severity and Outcome Rating System
qRT-PCR	quantitative real-time reverse transcriptase-polymerase chain reaction
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SpO_2	peripheral capillary oxygen saturation
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the final analysis of efficacy and safety of the investigational compound lumicitabine (also known as JNJ-64041575 and ALS-008176) of Study 64041575RSV2004. The SAP is to be interpreted in conjunction with the protocol.

A detailed analysis plan for the Interim Analysis will be described in the Interim Analysis Plan (IAP). A detailed analysis plan for the pharmacokinetic and pharmacokinetic/pharmacodynamics data will be described in a Clinical Pharmacology Analysis Plan (CPAP).

1.1. Trial Objectives

Primary Objective

The primary objective is to determine in hospitalized infants and children who are infected with Respiratory Syncytial Virus (RSV) the dose-response relationship of multiple regimens of lumicitabine on antiviral activity based on nasal RSV shedding using quantitative Real-time Reverse Transcriptase-Polymerase Chain Reaction (qRT-PCR).

Secondary Objectives

The secondary objectives are to determine in hospitalized infants and children who are infected with RSV:

- The safety and tolerability of lumicitabine.
- The PK of JNJ-63549109 in whole blood.
- The impact of lumicitabine on the clinical course of RSV infection.
- The impact of lumicitabine on the duration and severity of signs and symptoms of RSV infection as assessed by the Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS) questionnaire completed by the clinician in the electronic clinical outcome assessment (eCOA) device.
- The impact of lumicitabine on the time to undetectable nasal RSV viral load.
- The impact of lumicitabine on the emergence of RSV strains with resistance-associated mutations.
- The relationship between the pharmacokinetic (PK) of JNJ-63549109 and the pharmacodynamic (PD) (antiviral activity, clinical symptoms, and selected safety parameters) after single loading dose (LD) and repeated oral maintenance dose (MD) of lumicitabine.
- The acceptability and palatability of the lumicitabine formulation.

Exploratory Objectives

The exploratory objectives are to evaluate in hospitalized infants and children who are infected with RSV:

- The relationship between viral load and clinical outcome, including the relationship between RSV RNA levels and:

  - Requirement for and duration of supplemental oxygen.
  - Time to hospital discharge or readiness for hospital discharge, with readiness for discharge as evaluated by the investigator.
  - Time to clinical stability defined as the time from initiation of study treatment until the time at which the following criteria are met: return to pre-RSV infection status (hereafter referred to as "normalization") of blood oxygen level (without additional requirement of supplemental oxygen compared with pre-RSV infection status), normalization of oral feeding, normalization of respiratory rate, and normalization of heart rate.

- The relationship between viral load and duration and severity of signs and symptoms of RSV infection as assessed by the PRESORS questionnaire completed by the clinician in the eCOA device.
- The impact of the baseline viral subtype and genotype on the antiviral activity.
- The impact of lumicitabine on the duration and severity of signs and symptoms of RSV infection as assessed by the PRESORS questionnaire completed by the subject's parent(s)/caregiver(s) in the eCOA device.
- The relationship between the clinician eCOA and parent(s)/caregiver(s) eCOA responses.
- Medical resource utilization.
- The impact of lumicitabine on the infectious viral load using a quantitative culture of RSV (plaque assay) may be performed in a central laboratory at timepoints selected by the virologist.
- The comparison of the RSV viral loads measured in the mid-turbinate nasal swabs and endotracheal samples from intubated subjects.

1.2. Trial Design

This is a randomized, double-blind, placebo-controlled, multicenter study of lumicitabine in hospitalized infants and children who are infected with RSV.

During the writing of this SAP Option A in the protocol was selected as the design of this study. Therefore option B is not discussed in the SAP.

1.2.1. Option A

Hospitalized infants and children who are infected with RSV will be randomly assigned to a treatment regimen in this study, with 60 subjects planned per regimen. At least 120 subjects are planned to be enrolled up to a maximum of 180 subjects. An effort will be made to enroll at least 90 subjects aged between 28 days and 24 months and at least 12 subjects aged between 24 and 36 months. The number of subjects with comorbidities will be limited to 20%; additional comorbid subjects aged between 24 and 36 months may be allowed to enroll if the 20% threshold is reached before 12 subjects aged between 24 and 36 months are enrolled into the study.

Subjects will be randomized in a 1:1:1 ratio to Regimen A, B, or C:

- Regimen A (low-dose lumicitabine): a single 40 mg/kg LD (Dose 1) followed by nine 20 mg/kg MDs (Doses 2 to 10) of lumicitabine, administered twice daily.
- Regimen B (high-dose lumicitabine): a single 60 mg/kg LD (Dose 1) followed by nine 40 mg/kg MDs (Doses 2 to 10) of lumicitabine, administered twice daily.
- Regimen C (placebo): those randomized to a placebo regimen are subsequently randomized in a 1:1 ratio (to match volumes) to either:
    - A single 40 mg/kg placebo LD (Dose 1) followed by nine 20 mg/kg MDs (Doses 2 to 10), administered twice daily.
    - A single 60 mg/kg placebo LD (Dose 1) followed by nine 40 mg/kg placebo MDs (Doses 2 to 10), administered twice daily.

An IDMC (refer to Section 3.2, Independent Data Monitoring Committee, for details) will review the safety and PK data once the first 12 subjects and 30 subjects have completed treatment (Day 5/6) to assess if enrollment of additional subjects may safely continue in each arm. After at least 9 subjects have completed treatment with the 60 mg/kg LD/40 mg/kg MD lumicitabine regimen, the IDMC may recommend that sparse PK sampling be used for the other subjects. Subject recruitment and enrollment may continue while the data are being reviewed.

Subjects who are admitted to hospital due to RSV infection, including those who are otherwise healthy and those with underlying comorbidities (prematurity at birth [subject's gestational age was <37 weeks; for infants <1 year old at randomization], bronchopulmonary dysplasia, congenital heart disease, other congenital diseases, Down syndrome, neuromuscular impairment, or cystic fibrosis) can participate. However, enrollment of subjects with comorbidities can only start after at least 9 subjects have completed treatment with the 60 mg/kg LD/40 mg/kg MD lumicitabine regimen, after their safety and PK data have been reviewed by the IDMC, and after the IDMC has recommended that the recruitment of subjects with underlying comorbidities may start. Screening should be completed as soon as possible and the subject randomized within ≤5 days of RSV symptom onset. Procedures that are standard of care and performed within approximately 72 hours prior to randomization may be used in determining study eligibility or determining baseline values.

Randomization will be stratified by duration of RSV symptoms from onset until time of randomization (≤3 days; >3 days to ≤5 days), and by presence or absence of at least 1 comorbid condition for severe RSV disease (prematurity at birth [subject's gestational age was <37 weeks; for infants <1 year old at randomization], bronchopulmonary dysplasia, congenital heart disease, other congenital diseases, Down syndrome, neuromuscular impairment, or cystic fibrosis).

Treatment with lumicitabine should be initiated as soon as possible but no later than 4 hours after randomization to maximize the opportunity for the compound to inhibit viral replication and potentially improve outcomes. The parent(s)/caregiver(s) will administer the study drug at home until all doses are administered if the subject is discharged prior to the completion of treatment. Subjects will be evaluated for a total of 28 days postrandomization. Depending on the discharge date, assessments will be completed either in the hospital or during outpatient visits. On Day 28,

all subjects will complete the study either as an inpatient or outpatient. The total study duration for each subject will be 28 days, screening phase not included.

The doses will not exceed those resulting in an expected average JNJ-63549109 plasma Area Under the Curve from time 0 to 24 hours after dosing (AUC_{0-24h}) of 20,000 ng.h/mL (or 25,200 ng.h/mL in whole blood), a limit that is 2.7-fold lower than the lowest systemic NOAEL observed in nonclinical toxicity studies.

Assessments performed during the study will include: antiviral activity and an evaluation of the clinical course of RSV infection; safety and tolerability assessments (AEs, laboratory assessments, ECGs, physical examination, and vital signs/SpO_2); PK assessments based on sparse sampling will be performed using a popPK model; sequence analysis of the L-gene to identify preexisting sequence polymorphisms, to characterize RSV variants and other regions of the RSV genome if warranted, and to evaluate emergence of any resistance-associated mutations; and exploratory biomarkers to determine the effects of lumicitabine on markers of RSV disease.

Given the challenges of assuring study-site preparation in time to recruit for an acute seasonal infection like RSV and the delays caused by implementing an amendment during an RSV season, the duration of dosing of lumicitabine may be modified by recommendation of the IDMC based on the review of this study and data from other ongoing studies of lumicitabine.

Up to 2 formal interim analyses may be performed during the study. The first interim analysis will be performed once 36 subjects with ≤3 days of RSV symptoms have completed treatment (Day 5/6) or once 90 subjects with >3 to ≤5 days of RSV symptoms have been enrolled and have completed treatment. The following situations will be considered based on the results at this stage: that the study is considered futile; that superiority can be concluded; that subjects with >3 to ≤5 days of RSV symptoms at randomization may not achieve benefit (which may also be limited to ≤4 days of onset to symptoms); or that the study can continue unchanged. The treatment regimen may be modified after the first interim analysis, including increasing the treatment duration up to 10 days. After this analysis, randomization to 1 of the lumicitabine doses may be discontinued, the randomization ratio may change, and the study may not continue in subjects with >3 to ≤5 days of RSV symptoms at randomization. The second interim analysis may be performed at the discretion of the sponsor once at least 120 subjects have completed treatment (Day 5/6) (or at least 60 subjects with ≤3 days of RSV symptoms). The following situations will be considered based on the results at this stage: that the study is considered futile; that superiority can be concluded; or that the study can continue unchanged. Based on the recommendations of the IDMC following these interim analyses/reviews of PK, efficacy, and safety data, changes to randomization ratios in the treatment arms or an increase in treatment duration to 10 days may be implemented.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that there is a positive dose-response relationship of active treatment on the average RSV viral load AUC over 7 days, meaning that either the average AUC on the pooled active treatments is lower than on placebo, or the average AUC on the high dose is lower than the average AUC on placebo, using multiple contrast testing.

1.4. Sample Size Justification

On high dose, the hypothesis of the lumicitabine antiviral activity assumes a viral load reduction on the AUC of the log viral load over 7 days of at least 30% when compared to placebo in subjects with onset of symptoms ≤3 days and of at least 20% in subjects with onset of symptoms >3 days. The antiviral activity on low dose is assumed to be 80% when compared to the antiviral activity on the high dose. The positive dose-response relationship assumes that dose regimens with higher exposure with respect to MD will have at least an equal or better effect on viral load. Therefore 2 contrasts will be tested at each of the interim analysis points and final analysis; a contrast with no difference between the 2 active regimens tested against placebo (high equal to low, better than placebo) and a contrast with a positive 'linear' dose-response relationship (high better than low, low better than placebo) with respect to active regimens (where the effect of the low dose is exactly in between that of placebo and the high dose regimen). With respect to multiple contrast testing, multiplicity (2 contrasts) will be controlled at the prespecified (interim) alpha level by calculating adjusted p-values from the simulated distribution of the maximum or maximum absolute value of a multivariate t random vector (ie, using the correlation between the contrasts to optimally control for alpha).

Based on the observed data of other in-house studies, the estimated SD is assumed to be approximately 34% of the AUC for subjects treated with placebo and the SD is equal in each of the treatment regimens. The overall (family wise) type 1 error rate of 2.5% (1-sided) will be adjusted for multiple testing due to formal interim analyses using a Pocock alpha spending function with 3 sequential tests (2 interim, 1 final). Based on 10,000 simulations and using a general linear model with treatment regimen as fixed factors, and under the assumption that 40% of the recruited subjects have onset of symptoms ≤3 days, a sample size of 180 subjects randomized in a 1:1:1 ratio will offer approximately 97% power to detect a positive dose-response relationship using multiple contrast testing. With the second interim analysis planned after at least 120 subjects, there will be at least 80% power to detect a positive dose-response relationship at the time of this analysis.

1.5. Randomization and Blinding

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned based on a computer-generated randomization schedule prepared before the start of 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 duration of RSV symptoms from onset till time of randomization (≤3 days versus >3 to ≤5 days) and by presence or absence of comorbidity. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

Data that may potentially unblind the treatment assignment (ie, study drug serum concentrations, study drug preparation/accountability data, treatment allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until the unblinded IDMC review takes place (see Section 3.2, Data Monitoring Committee). The blind will be broken for the interim analyses (see Section 3.1, Interim Analysis) or when all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is strongly recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF) and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. Discontinuation of study treatment should be done only for the reasons stated in the Protocol Section 10.2, Discontinuation of Study Treatment/Withdrawal From the Study; unblinding of study treatment should not necessarily lead to study drug discontinuation.

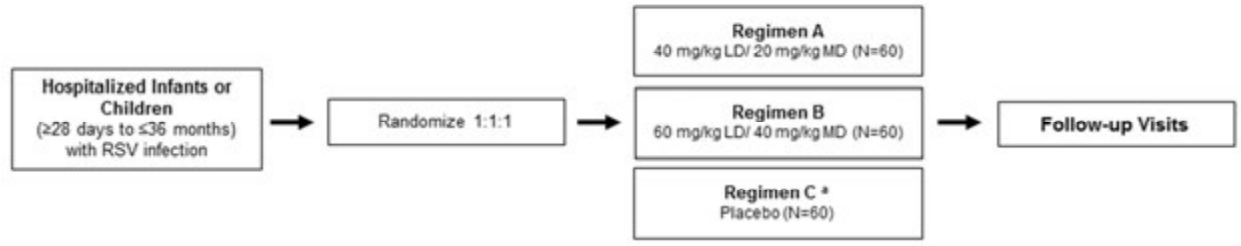
In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed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

In the event that the subject continues into the long-term follow-up study, then the subject and investigator will remain blinded until the follow-up study is completed.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows and Phase Definition

Figure 1: Schematic Study Overview: Option A



Abbreviations: LD: loading dose; MD: maintenance dose; RSV: respiratory syncytial virus.
a. Subjects randomized to placebo will be subsequently randomized in a 1:1 ratio to the placebo regimen matching Regimen A or Regimen B.

Phases will be constructed as follows:

Trial phase	Start date	End date
Pre-screening	Date time of first assessment, taken as part of standard of care within 84 hours* prior to randomization	1 minute before start of screening phase
Screening	00:00 of the date of signing the informed consent	1 minute before the first study medication intake
Treatment	Date time of first study medication intake	Date time of last investigational medication intake + 72 hours
Follow-up	End of Treatment phase + 1 minute	Trial termination date (date of last contact) with timestamp 23:59.

*In order to account for "approximately" 72 hours prior to randomization

The last phase, whichever it is for a subject, always ends on 23:59 of the day of trial termination (last contact) in study 64041575RSV2004. Note a subject can volunteer for long-term follow-up, in this case the subject will be enrolled in study 64041575RSV2002.

Assessments will be assigned to phases based on their date time, seconds will be ignored. If the day part of the start date of the assessment is present but the time part is missing, the assessment will be allocated as if it started at 00:00h on the day of the assessment (unless for Adverse Events see details in section 6.1.1). If the day part of the end date of the assessment is present but the time part is missing, no formal imputation will be done, but these rules will only be applied in order to be able to allocate assessments to phases. The assessment will be allocated as if it happened at 23:59h on the day of the assessment.

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit.

All visits (regardless the investigated parameter) will be allocated to analysis visits based on the day relative to the start of study medication:

Target Day	Analysis visit (numeric version)	Analysis visit	Day Interval
-∞	-1	Screening	<=1[1]
1	0	Baseline	<=1[2]
1	1	Day 1	[1][3]
2	2	Day 2	[2]
3	3	Day 3	[3]
4	4	Day 4	[4]
5	5	Day 5	[5]
6	6	Day 6	[6]
7	7	Day 7	[7,9]
10	10	Day 10	[10,12*]
14	14	Day 14	[12*,20]
+∞	28	Day 28	[21,+∞[

[1] Records before the datetime of first intake only.
[2] As calculated according to the baseline definition.
[3] Includes only the post-dose records.
* Depending on the VISIT label, the measurement of subjects returning on Day 12 should be assigned to Day 10 or Day 14. In case the VISIT label equals Day 12 the measurement will be allocated to Day 10.

For the analyses of measurements scheduled once daily the following rules will be applied in order to have only one evaluation per subject per analysis visit:

1. If two assessments fall within the same interval, the measurement closest to the target day will be used.
2. If the assessments are equidistant, the last measurement within the interval will be used.
3. If there are two measurements on the same date and time, then the measurement with the highest sequence number will be used.

An exception will be made:

1. In case multiple nasal swabs were taken on a single day, the maximum viral load on the log scale will be used as the analysis value for that subject on that day.

For the analysis of measurements scheduled more than once daily (vital signs: twice daily and SpO_2: every 4 hours / every 8 hours), the assessments will be allocated to analysis time points as described in the table below based on the actual time of the measurement. In case there is more than one assessment per analysis time point window, the mean of these assessments will be calculated in order to have only one evaluation per analysis timepoint.

Analysis time point (numeric version)	Analysis time point	Time Interval (hour:min)
Vital sign assessments *		
1	Morning	]02:00, 14:00]
2	Evening	]14:00, 02:00]
SpO_2**		
0	Morning	]0:00, 08:00]
8	Midday	]08:00, 16:00]
16	Evening	]16:00, 0:00]

* In case the measurement should be allocated to 'Evening' of the previous day based on the time interval, the analysis visit should be adapted based on the relative day of the previous day. In case less than 75% of subjects is inpatient on an analysis visit, the records will not be allocated to any time point. In this case, the average of all records on that day (selected according to the rules for the analysis visit defined above) will be used for the analysis in case multiple records are available. In case 75% or more subjects are inpatient on this analysis visit, all records will be assigned to an analysis time point (also subjects for which the visit is outpatient) and both time points will be analyzed.

** For the SpO_2, the analysis time point will be set to Midday on outpatient visits of individual subjects, without taking the actual time into account. In case at least 75% of subjects is still in inpatient on this analysis visit, all 3 time points will be used and shown in the analysis. In case less than 75% of subjects is inpatient, only the Midday time point will be analyzed.

2.2. Pooling Algorithm for Analysis Centers

If positive treatment effects are found in a trial with appreciable numbers of subjects per center, there should generally be an exploration of the heterogeneity of treatment effects across centers, as this may affect the generalizability of the conclusions. As it is expected that for this trial subjects will be recruited over a large number of centers with a small number of subjects per study center, there is no need to check for treatment by center interactions. In addition, the primary endpoint is an objective endpoint, which is evaluated by a central viral monitor, and thus, no heterogeneity across centers is anticipated. Therefore, no pooling algorithm for analysis centers will be specified.

2.3. Analysis Sets

2.3.1. All Randomized Analysis Set

Randomized Analysis Set (RAND): All randomized subjects with a randomization date at or before the date of first intake of medication, or with a randomization date and a missing date for first medication intake, analyzed as randomized.

2.3.2. Efficacy Analysis Set(s)

Intention-To-Treat (ITT) set: All randomized subjects who receive at least 1 dose of study drug. Analyses on the ITT Set will be analyzed as randomized.

Intention-To-Treat-infected (ITT-i) set: All randomly assigned subjects who receive at least 1 dose of study drug and who have an RSV infection confirmed by a PCR-based assay at baseline or within 1 hour after the first study medication intake at the central laboratory. Analyses on the ITT-i Set will be as randomized.

Per-Protocol (PP) Analysis set: All subjects in the ITT-i set who do not have protocol violations that may have an impact on the efficacy analysis.
Decisions regarding which subjects are included in the PP set will be made before database lock on following criteria:

- Compliance: Subjects must have at most 1 missed dose. On the day of randomization at least one dose needs to be taken (so missed dose cannot be the first dose).
- The actual treatment must be the same as the planned treatment.
- No unblinding may have taken place during the study.
- Subjects will be excluded from the PP set if they have taken concomitant medications that may have affected the efficacy of the trial medication. Subjects will be excluded on a case by case basis using a list provided by clinical.
- Subjects may not violate inclusion criteria 3 or 4, nor exclusion criteria 1, 3, 4, 5, 6, 9 or 10.

Analyses on the Per-Protocol set will be analyzed as randomized.

2.3.3. Safety Analysis Set

Safety Set or All Subjects Treated (AST): All subjects who received at least 1 dose of study drug, analyzed as treated.

Randomized or Treated (RT) set: All subjects who are in the Randomized Analysis Set (RAND) and/or the All Subjects Treated (AST) set. The Randomized or Treated Analysis Set (RT) will be used in all listings.

2.4. Definition of Subgroups

Following subgroups will be used for the Efficacy analysis (primary and selected secondary endpoints):

- Onset time of RSV symptoms (≤3 days, >3 days - ≤5 days)
- Baseline RSV subtype

- Region [Japan, non-Japan] Note: Japan region only includes subjects indicated as Japanese on the CRF.
- Baseline RSV Viral load [<=C log_{10} copies/mL, >C log_{10} copies/mL] with C = rounded median
- Presence of underlying comorbidity (yes, no)

Medical review will be done immediately before data base lock on a list with unique coded medical history terms (MedDRA Preferred Terms) to indicate which subjects had comorbidities. The following list of comorbid disease will be identified and potentially analyzed for efficacy (in case at least 15 subjects are enrolled in each of the subgroups):

- Comorbid diseases for severe RSV disease
  - BPD (bronchopulmonary dysplasia) [Yes/No]
  - CHD (congenital heart disease) [Yes/No]
  - Other Congenital disease [Yes/No]
  - Down syndrome [Yes/No]
  - Neuromuscular impairment [Yes/No]
  - Cystic fibrosis [Yes/No]
- Other conditions/therapy of potential interest due to risk of infections in general:
  - Type I diabetes [Yes/No]
  - Use of systemic corticosteroids (PO, IV) prior to or during the treatment phase

[Yes/No], based on medical review on a list with unique coded concomitant medications.

The following subgroups will be investigated for safety (complete safety for region, selected summary tables for age category):

- Region [Japan, non-Japan] Note: Japan region only includes subjects indicated as Japanese on the CRF.
- Age category [28 days-24 months; > 24 months to <= 36 months]

2.5. Study Day and Relative Day

Study Day 1 refers to the date of first study medication intake (reference day). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

The relative day for a visit is defined as:

reldy = visit day – reference day+1

for visits on or after the reference day, and

reldy = visit day – reference day

for visits before the reference day, where the reference day is the start of study medication.

There is no 'Day 0'.

2.6. Baseline

The baseline record is derived as the last record before the first intake of the study drug. The baseline record will be duplicated and assigned to the treatment phase.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

An Interim Analysis Committee will be responsible for performing the formal interim analysis and will consist of sponsor personnel who are not otherwise involved in the study. The IDMC will review the data and make recommendations to the Sponsor Committee, which will be responsible for identifying appropriate actions based on the recommendations of the IDMC.

Two types of interim analyses are distinguished: formal interim analysis and interim analyses performed by the IDMC only. The IDMC is described in Section 3.2, Independent Data Monitoring Committee, and Section 3, Overview of Study Design. At any formal interim analysis, the IDMC will also perform a data review.

The Interim Analysis Committee will be responsible for performing any formal interim analysis and will consist of sponsor personnel who are not otherwise involved in study activities. The first formal interim analysis will be performed when 36 subjects with ≤3 days of RSV symptoms have completed treatment or when 90 subjects with >3 to ≤5 days of RSV symptoms have been enrolled and have completed treatment. The second interim analysis may be performed at the discretion of the sponsor when at least 120 subjects have completed treatment (or at least 60 subjects with ≤3 days of RSV symptoms), which may allow an analysis at the end of a season.

The following situations will be considered based on the results of any formal interim analysis: that the study is considered futile; that superiority can be concluded; that subjects with >3 to ≤5 days of RSV symptoms at randomization may not achieve benefit (which may also be limited to ≤4 days of onset to symptoms); that the treatment duration needs to be increased to up to 10 days; or that the study should continue unchanged. In the case of the (unbinding) futility boundary or the superiority boundary being crossed, the IDMC may recommend early termination to the Sponsor Committee. If early superiority on the primary endpoint can be established, the study may be continued in order to accumulate data to allow the selection of the dose regimen or further substantiate the benefit-risk profile in this population; in this case the randomization ratio of active to placebo treatment may be altered for example, if dose selection is evident from the dose-response analysis, subjects randomized to active treatment may all receive the optimal dose. Alternative randomization ratios can be endorsed by the IDMC and implemented by the Sponsor Committee for Option A are 1:2:0, 1:0:2, 1:2:2, and 2:1:3 for the placebo, low dose, and high dose, respectively.

Results of the formal interim analyses can be used in interactions with Health Authorities.

3.2. Independent Data Monitoring Committee

An IDMC will be established to monitor data and will review data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in this study. The IDMC will review the data and make recommendations to the Sponsor Committee, which will be responsible for identifying appropriate actions based on the recommendations of the IDMC. Details are provided in the IDMC Charter.

The IDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician, 1 of whom will chair the committee. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter. Other members may be required dependent on the nature of the interim analysis. The intent is to have the same IDMC monitoring this study as for Study ALS-8176-503 given their familiarity with the compound. The IDMC will make dose recommendations at the beginning of the study, which will help determine which design option is chosen.

The IDMC will review the PK and safety data at the timepoints specified in Section 3, Overview of Study Design, and will continue to assess the PK, safety, and (selected) efficacy data during the conduct of the study. The frequency of IDMC reviews will be detailed in the IDMC Charter. At any formal interim analysis, the IDMC will also perform a data review.

Given the challenges of ensuring study-site preparation in time to recruit for an acute seasonal infection like RSV and the delays caused by implementing an amendment during an RSV season, the duration of dosing of lumicitabine may be modified by recommendation of the IDMC based on the review of this study and data from other ongoing studies of lumicitabine. The duration of dosing if extended will not exceed 10 days and the doses will not exceed those resulting in an expected average JNJ-63549109 plasma $AUC_{0\text{-}24h}$ of 20,000 ng.h/mL (or 25,200 ng.h/mL in whole blood), a limit that is 2.7-fold lower than the lowest systemic NOAEL exposure observed in nonclinical toxicity studies. If the IDMC determines that subjects with a duration of RSV symptoms of 5 days prior to randomization may not achieve benefit based on interim results, they may recommend that the time of onset of RSV symptoms to the time of randomization is reduced. In addition, if the IDMC determines that subjects with a duration of RSV symptoms longer than 5 days prior to randomization may achieve benefit, this duration may be increased to up to 7 days (ie, 7 days from symptom onset to randomization). If such modifications, including changes to the randomization ratio, are recommended by the IDMC and endorsed by the Sponsor Committee, these changes will be communicated in writing to investigators, health authorities, and IEC/IRB and may be implemented without amendment to this protocol. Sponsor personnel involved in this process will not be involved in the conduct of the study. Details are provided in the IDMC Charter.

4. SUBJECT INFORMATION

Subject information will be analyzed on the safety set (AST) and the Intention-To-Treat-infected (ITT-i) set, unless specified otherwise for a specific display.

4.1. Demographics and Baseline Characteristics

All demographics and baseline characteristics will be summarized overall and by treatment group. Descriptive statistics and frequency distribution will be provided for respectively the continuous and categorical parameters here below.

Demographic parameters:

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- Geographic region (based on country: North America [to include Puerto Rico], Europe, South America, Asia-Pacific)
- Region (Japan, non-Japan) Note: Japan region only includes subjects indicated as Japanese on the CRF.
- Age (months)
- Age category [≥28 days to <24 months, ≥24 to <=36 months]
- Weight at baseline (kg)
- Weight at baseline (kg) quartiles [1st Quartile, 2nd Quartile, 3rd Quartile, 4th Quartile]
- Height at baseline (cm)
- Height at baseline (cm) quartiles [1st Quartile, 2nd Quartile, 3rd Quartile, 4th Quartile]
- BMI at baseline (kg/m^2) = Weight at baseline (kg) / (Height at baseline (m))^2 (rounded to 1 decimal. Even if available in the raw data, BMI will be recalculated from baseline weight and height)
- BMI at baseline (kg/m^2) quartiles [1st Quartile, 2nd Quartile, 3rd Quartile, 4th Quartile] for each of the age categories

Baseline disease characteristics:

- Duration of RSV symptoms from onset till time of randomization (days)
- Duration of RSV symptoms from onset till time of randomization (days) categories (≤3 days; >3 days to ≤5 days)
- Presence comorbid conditions (yes, no)
- Number of subjects with one of following comorbid conditions:
    - prematurity at birth [subject's gestational age was <37 weeks; for infants <1 year old at randomization],
    - bronchopulmonary dysplasia,
    - congenital heart disease,
    - other congenital diseases,
    - Down syndrome,
    - neuromuscular impairment, or
    - cystic fibrosis

- Baseline RSV Viral load (log_{10} copies/mL)
- Baseline RSV Viral load [<=C log_{10} copies/mL, >C log_{10} copies/mL] with C = rounded median
- Baseline RSV subtype
- Receiving Supplemental Oxygen (yes, no)
- Reasons for hospitalization (PRESORS question 1)

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized overall.

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

- subjects randomized, randomized and not treated, treated and not randomized, randomized or treated, safety set, intent-to-treat set, intent-to-treat-infected set and per-protocol analysis set.
- subjects who completed and discontinued treatment and the trial, with the reasons of discontinuation.
- subjects per phase and per analysis visit in the trial

4.3. Treatment Compliance

Treatment compliance will be calculated for the loading dose and maintenance dose separately. The 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 (including additional doses needed because of treatment extension)

The planned number of doses is 1 loading dose and 9 maintenance doses. In case of treatment extension the maximum planned number of doses for the maintenance doses will be 19.

Treatment compliance will be summarized descriptively by treatment group.

4.4. Extent of Exposure

Descriptive statistics for treatment duration will be presented by treatment group.

The treatment duration is defined as date/time of last study drug intake – date/time of first study drug intake + 72 hours.

Note: treatment interruptions will not be taken into account for the above definition.

4.5. Protocol Deviations

Only major protocol deviations will be defined in this trial. All major protocol deviations will be listed, including the deviations to the inclusion-exclusion criteria, and the violations to the prohibitions and restrictions, if any. A tabulation of the number and percentage of subjects per major protocol deviation will be provided

Note that the Per-protocol set definition takes into account any deviation from the protocol that could affect the efficacy. These are not necessarily major deviations, nor are major deviations considered to always affect efficacy and to warrant exclusion from the PP analysis.

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be summarized by preferred term using the World Health Organization Drug Dictionary (WHO-DD) as frequency tables in 2 parts:

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.

Separate tables will be made for medication related to fever and not related to fever. Medication related to fever will be categorized as Acetaminophen/paracetamol, Ibuprofen, or other. These tables will be made by phase and combined phases and by treatment group and overall treatment.

4.7. Medical History

The medical history records will be listed; separate listings will be generated for conditions of interest (allergic/immunologic, dermatological)

5. EFFICACY

All efficacy will be analyzed on the Intention-To-Treat-infected (ITT-i) set.

5.1. Analysis Specifications

5.1.1. Level of Significance

Two contrasts will be tested at each of the interim analysis points and final analysis; a contrast with no difference between the 2 active regimens tested against placebo (high equal to low, better than placebo) and a contrast with a positive 'linear' dose-response relationship (high better than low, low better than placebo) with respect to active regimens (where the effect of the low dose is exactly in between that of placebo and the high dose regimen). With respect to multiple contrast testing, multiplicity (2 contrasts) will be controlled at the prespecified (interim) alpha level by calculating adjusted p-values from the simulated distribution of the maximum or maximum absolute value of a multivariate t random vector (ie, using the correlation between the contrasts to optimally control for alpha).

The significance level of *alpha* (α*) will have to be calculated based on the information fraction at the time of the test using the pre-specified Pocock α spending function.

$$\alpha^*(t') = \alpha \cdot \ln(1 + (e-1)t')$$

where t'=n/N, n is the ITT-i set size and N is the expected ITT-i set size at the end of study (=120).

5.1.2. Data Handling Rules

For analysis purposes the $\log_{10}$ qRT-PCR viral load will be imputed with 0 when the result is 'negative', and the midpoint on the $\log_{10}$ scale between the limit of detection and limit of quantification when the result is 'positive' but non-quantifiable. For the qRT-PCR assay used for detection and quantification of RSV-A and RSV-B, the lower limit of quantification (LLOQ) is 3 $\log_{10}$ (copies/mL) for RSV-A and 2.4 $\log_{10}$ (copies/mL) for RSV-B, the limit of detection (LOD) is 2.7 $\log_{10}$ (copies/mL) for RSV-A and 1.9 $\log_{10}$ (copies/mL) for RSV-B.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

RSV RNA will be measured in mid-turbinate nasal swab specimens using an RSV-A/B qRT-PCR developed by DDL Diagnostic Laboratory.

The primary endpoint is RSV RNA $\log_{10}$ viral load (measured by qRT-PCR in the mid-turbinate nasal swab specimens) area under the concentration-time curve (AUC) from immediately prior to first dose of study drug (baseline) until Day 7.

The primary estimates of the $AUC_{1\text{-}7\ Days}$ will be derived from a mixed model (see section 5.2.3 for the detailed specification). No imputations of missing data from nasal swabs post-baseline will be done in this model, as this mixed model would allow to make inferences under the missing at random assumption.

Note that for the primary endpoint the following rules apply:

- Only values as provided by the central lab will be used.
- Baseline is defined as the last measurement before first intake. In case a result is available that is no later than 1 hour after treatment initiation this may be used but only if no pre-treatment observation is available.
- For all post-baseline analysis visits the RSV RNA $\log_{10}$ viral load result of the swab that was performed at that day will be used.
- In case multiple nasal swabs were taken on a single day the maximum on the log scale will be used as the value for that subject.

As a sensitivity analysis, descriptive statistics will be provided for the viral load AUC between 0h and 144h ($AUC_{0\text{-}144h}$); calculated by the trapezoidal summation rule, based on date time of sampling, including the timepoints with (imputed) values available:

$$AUC_{0-144\text{h}} = \frac{1}{2}\sum_{i=1}^{n}(y_i + y_{i-1}) \times (t_i - t_{i-1})$$

where i=1,2,3,…n are the time points when post baseline samples are collected, y_i is the log 10 viral load at the time and t_i is the time in hours post baseline. y_o is the (imputed) log 10 viral load at baseline, t_0 is time 0 and tn is time 144h.

The following additional rules, on top of the rules of the primary analysis, will be applied to deal with missing values before calculating the Viral load AUC $_{0\text{-}144h}$:

- The value at time point 0h, if not exactly at 0h, will be calculated based on intrapolation between the last observed pre-dose value and the first observed post-dose value.
- The value at 144h, if not exactly at 144h, will be calculated based on intrapolation between the last observed value before 144h and the first observed value after 144h.
- Missing values between 0h and 144h will be imputed by intrapolation.
- If the last observation is missing, the last available observation will be carried forward until 144h is reached.

5.2.2. Estimand

The difference in the RSV RNA $\log_{10}$ viral load $AUC_{1\text{-}7Days}$ for active versus placebo treatment will be derived from the mixed model specified in section 5.2.3, deriving least square mean differences, including the nominal 95% 2-sided confidence intervals in the Intention-To-Treat-infected (ITT-i) set.

These estimates are customary and will not be used to conclude for a positive dose-response relationship, but are relevant for reviewers to understand the effect of each dose on the viral load and the customary level of uncertainty associated with it.

5.2.3. Analysis Methods

Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, stratification factors, analysis visit, and treatment-by-analysis visit interaction, as well as the continuous, fixed covariates of 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 will not converge, the following list of covariance structures will be applied and a selection will be based on the Akaike Information Criterion for those that do converge:

- Unstructured [UN]
- Ante-dependence [ANTE(1)]
- Heterogenous Toeplitz [TOEPH]
- Heterogeneous CS [CSH]
- Heterogeneous AR(1) [ARH(1)]
- Toeplitz [TOEP]

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The testing of the dose-response relation is based on the expectation that higher dose regimens will be at least as efficacious as lower dose regimens with respect to efficacy on the viral load over time. Therefore, two contrasts on the dose regimens have been selected that are consistent with this expectation:

- a contrast with no difference between the 2 active regimens tested against placebo and
- a contrast with a positive linear dose-response relationship with respect to active regimens.

A multiple comparison approach will be taken testing the 2 contrasts combined versus placebo, adjusted for multiplicity.

The SAS mock code used to test the primary hypotheses will be as follows:

```
proc mixed data=viral_load;
      where avisitn in (2,3,4,5,6,7)
      class avisitn trt usubjid stratum;
      model logtiter = trt|avisitn stratum base|avisitn /ddfm=kr s;
      repeated avisitn/subject=usubjid type=un;
      lsmestimate trt*avisitn
      "Plateau" -4 2 2 -4 2 2 -4 2 2 -4 2 2 -4 2 2 -2 1 1,
      "Linear" -4 0 4 -4 0 4 -4 0 4 -4 0 4 -4 0 4 -2 0 2
      /divisor=4 adjust=simulate seed=3369 alpha=α* lower cl;
run;
```

The variable *trt* denotes the *placebo, low dose regimen*, and *high dose regimen* treatment groups, the *avisitn* variable denotes the swabbing visits at Days 2 through 7, and the *base* variable is the baseline log_{10} viral load measured at Day 1.

The *lower* option is selected as the contrast needs to have a value below zero (ie, there needs to be a reduction in $AUC_{1\text{-}7Days}$ comparing active treatment to placebo). In summary, a positive dose-response relationship will be concluded if based on this analysis for any of the two estimations the resulting adjusted p-value is lower than the associated Pocock critical value (see section 5.1.1).

The differences in the $AUC_{1\text{-}7Days}$ for active versus placebo will be derived using appropriate contrasts deriving least square mean differences, including the 95% 2-sided confidence intervals.

The individual $AUC_{0\text{-}144h}$ as calculated using the trapezoidal rule will be considered as a supportive analysis and will be analyzed using a linear model with $AUC_{0\text{-}144h}$ as a dependent variable and treatment group and stratum as fixed factors, and baseline log_{10} viral load as fixed covariate. For this analysis no adjustments for multiplicity will be applied, that is the differences versus placebo will be estimated using appropriate contrasts with 95% confidence intervals.

Before unblinding, the viral load data will be evaluated to assess whether viral load measurements based on swabs performed by the Health Care Provider (HCP) are similar as the swabs not performed by a HCP. Individual line plots will be created to visually check individual patterns for any difference between the samples. Depending on the visual inspection a decision will be made if all samples or only the samples from swabs performed by a HCP will be considered for the primary analysis. For example, if for the majority of subjects there is a clear drop in viral load when switched from samples taken by a HCP and samples taken by a non-HCP, the decision could be that only samples from swabs done by a HCP will be used. This blinded data review will be done before the database lock of the interim analysis and may also take other data sources into account.

5.3. Secondary Endpoints

5.3.1. 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.

5.3.1.1. RSV RNA log_{10} viral load (qRT-PCR)

Table 1: Calculations and Conversion Formulae

Measurement	Formula
Log_{10} viral load actual values	Log_{10} of the actual values as measured with qRT PCR
Log_{10} viral load	Change = Log_{10} viral load actual value – log_{10} baseline value

change from baseline	
Peak viral load	Highest value of log_{10} viral load at or after the baseline measurement. The first record in time with this highest value is selected. This can be the baseline record or an unscheduled record.
Rate of decline of viral load over the first 24 hours	Calculated as a log decline/24 hours defined as: (24-hour log viral load after first dose of study drug – log viral load at baseline) / (date/time of 24-hour viral load sample – date/time of baseline viral load) Note, the 24-hour viral load may not have been measured at exactly 24 hours following first dose, but the actual date/time associated with the 24-hour viral load will be used in computing the viral load slope. In case the 24 hour measurement is not available the slope will be calculated using the Day 3 assessment (48 hours), using the same definition. If there is no measurement in that time frame, the slope will not be calculated.
RSV viral load $AUC_{0\text{-}240h}$ RSV viral load $AUC_{0\text{-}336h}$ [trapezoidal method]	Idem as RSV viral load $AUC_{0\text{-}144h}$ from 0 hours until 144 hours using the trapezoid method (sensitivity analysis), but from 0 hours until 240 hours and 336 hours respectively.
RSV viral load $AUC_{0\text{-}xxh}$ [trapezoidal method]	Idem as RSV viral load $AUC_{0\text{-}144h}$ using the trapezoid method, but from 0 hours until xx hours, where xx will be calculated as 24 times the number of days with treatment + 1 day.
Time to peak viral load (hours) [Time-to event]	The time from initiation of study treatment until the first time point with the peak viral load (= event). Subjects for which the peak was reached at the baseline measurement will have time 0. Subjects for whom the peak is reached at the last observed time point will be censored at that time point. Subjects for which this last assessment is the baseline assessment will be censored at time 0. (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 (<LOD) Detectable (<LOQ) Quantifiable (>= LOQ)
Viral load status at each time point (binary)	Each RSV viral load measurement will be assigned to one of the 2 categories to identify if it is undetectable. Categories will be Yes (1) or No (0).
Time to virus undetectable (hours) [Time-to event]	The time in hours from initiation of study treatment until the first post baseline time point at which the virus is undetectable in an assessment and after which time no detectable virus assessment follows (= event). For each subject in the ITT-i it will be assumed that the subject is detectable or quantifiable at baseline (even if the value is negative). Subjects will be (right-) censored at the last time observation of a detectable viral load. Subjects for which this last assessment is the baseline assessment will be censored at time 0. (Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal.
Time to virus undetectable (hours) [interval censored]	The time in hours from initiation of study treatment until the first post baseline time point at which the virus is undetectable, using interval censoring. The boundaries of the censoring intervals are defined as the number of hours from the start of treatment. The left boundary of the interval is the last positive assessment before the first confirmed negative sample which is not followed by a confirmed positive sample (at baseline every subject is considered positive). If no negative samples are observed, the left boundary will be the last sample obtained. The right boundary of the interval is the first confirmed negative sample which is not followed by a confirmed positive sample. If this is not observed, the interval is right censored. A confirmed positive sample is defined as two consecutive non-negative samples; a confirmed negative sample is defined as two consecutive negative samples. Last obtained sample, whether positive or negative, is always

	considered confirmed.

5.3.1.2. RSV RNA log_{10} viral load plaque assay (exploratory endpoints)

Measurement	**Formula**
Log_{10} viral load actual values	Log_{10} of actual values as measured using a quantitative viral culture (plaque assay)
Log_{10} viral load change from baseline	Log_{10} of actual value – Log_{10} of baseline value

5.3.1.3. RSV clinical outcome

Measurement	**Formula**
Length of hospital stay (hours) [Time-to event]	The time from treatment initiation to hospital discharge (=event) in hours. Subjects who complete or withdraw from the study prior to the event will be censored at the date of completion or withdrawal. If the time is not available they will be censored at 12:00. In case of death the subject will be censored at the maximum observed number of hours until the occurrence of the event or censoring for all subjects achieving the event or being censored because of study completion or withdrawal. (Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal.
Time to readiness for discharge (hours) [Time-to event]	The time from study treatment initiation to readiness for discharge (= event) in hours, with readiness for discharge defined by the investigator. Derivation similar as “Length of hospital stay”
Length of hospital stay since hospital admission (hours) [Time-to event]	The time from hospital admission to hospital discharge (= event) in hours. Derivation of censoring similar as “Length of hospital stay”. (Date and time of event or censoring - date and time of hospital admission)/3600, rounded to one decimal

Measurement	**Formula**
Time to readiness for discharge since hospital admission (hours) [Time-to event]	The time from hospital admission to readiness for discharge (= event) in hours, with readiness for discharge defined by the investigator. Derivation similar as "Length of hospital stay since hospital admission"
Duration of intensive care unit (ICU) stay (hours) [Duration]	The total number of hours a subject stayed in ICU (= event) from first intake until study termination, calculated as sum of [(end date and time of event - start date and time of event)/3600], rounded to one decimal for all separate events per subject If the initial start time is prior to the first dose of study drug, the duration prior to the first dose of study drug will be deducted from the overall duration. If the end date is missing, the end date is considered to be after study completion or withdrawal. If the end date and time is after the study completion/discontinuation, the duration after the date and time of study completion/discontinuation will be deducted from the overall duration. If the time is not available it will be put at 12:00.
Requirement for intensive care unit (ICU) stay	Does the subject require admission to the ICU after first dose of study drug? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that were not in ICU before first dose of study drug.
Requirement for oxygen supplementation	Does the subject require any oxygen supplementation (noninvasive or invasive) after first dose of study drug? Oxygen supplementation is indicated on the Oxygen Supplementation form: Type of supplemental oxygen administration. Categories will be Yes (1) or No (0). Only derive this parameter for subjects that didn't require oxygen supplementation before first dose of study drug.
Requirement for noninvasive nonmechanical ventilation	Does the subject require noninvasive nonmechanical ventilation support after first dose of study drug? On the Oxygen Supplementation form, oxygen supplementation is

Measurement	**Formula**
support	indicated but the type of supplemental oxygen administration doesn't equal "Non-Invasive Mechanical Ventilation" or "Invasive Mechanical Ventilation"? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that didn't require oxygen supplementation before first dose of study drug.
Requirement for noninvasive mechanical ventilation support	Does the subject require noninvasive mechanical ventilation support after first dose of study drug, as indicated on the Oxygen Supplementation form: Type of supplemental oxygen administration equals "Non-Invasive Mechanical Ventilation"? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that didn't require noninvasive mechanical ventilation support or invasive mechanical ventilation support before first dose of study drug.
Requirement for invasive mechanical ventilation support	Does the subject require invasive mechanical ventilation support after first dose of study drug, as indicated on the Oxygen Supplementation form: Type of supplemental oxygen administration equals "Invasive Mechanical Ventilation"? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that didn't require invasive mechanical ventilation support before first dose of study drug.
Requirement for supplemental feeding/hydration	Does the subject require supplemental feeding/hydration (e.g. IV catheter/nasogastric tube) after first dose of study drug? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that didn't require supplemental feeding/hydration before first dose of study drug.
Time to end of intensive care	The time from first study drug intake until the time of

Measurement	**Formula**
unit (ICU) stay (hours) [Time-to event]	discharge from the ICU after which the subject was not readmitted to the ICU (= event) Subjects who complete or withdraw from the study prior to the event will be censored at the date of completion or withdrawal. If the time is not available they will be censored at 12:00. In case of death the subject will be censored at the maximum observed number of hours until the occurrence of the event or censoring for all subjects achieving the event or being censored because of study completion or withdrawal. If no admittance to the ICU was necessary, the value will be set to 0. (Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
Time to end of Oxygen supplementation (hours) [Time-to event]	The time from first dose of study drug start of oxygen supplementation to the last end date and time of any oxygen supplementation (= event) in hours (Oxygen supplementation is indicated on the Oxygen Supplementation form: Type of supplemental oxygen administration.). (Note: it is not necessary that the subject started on oxygen at baseline.) If the end date is missing, the end date is considered to be after study completion or withdrawal. Subjects who complete or withdraw from the study prior to the event will be censored at the date of completion or withdrawal. If the time is not available they will be censored at 12:00. In case of death the subject will be censored at the maximum observed number of hours until the occurrence of the event or censoring for all subjects achieving the event or being censored because of study completion or withdrawal. If no oxygen supplementation was necessary after first dose of study drug, the value will be set to 0 hours. (Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
Time to end of noninvasive mechanical ventilation support (hours) [Time-to event]	The time from first dose of study drug to the last end date and time of noninvasive mechanical ventilation and invasive mechanical ventilation support (= event) in hours. Noninvasive mechanical ventilation and invasive mechanical

Measurement	**Formula**
	ventilation are defined as indicated on the Oxygen Supplementation form: Type of supplemental oxygen administration. Derivation similar as "Time to end of Oxygen supplementation"
Time to end of invasive mechanical ventilation support (hours) [Time-to event]	The time from first dose of study drug to the last end date and time of invasive mechanical ventilation support (= event) in hours. Invasive mechanical ventilation support is defined as indicated on the Oxygen Supplementation form: Type of supplemental oxygen administration. Derivation similar as "Time to end of Oxygen supplementation"
Time to end of supplemental feeding/hydration (hours) [Time-to event]	The time from first dose of study drug to the last end date and time of supplemental feeding/hydration (e.g. IV catheter/nasogastric tube) (= event) in hours. Derivation similar as "Time to end of Oxygen supplementation"
Time to return to pre-RSV disease level for respiratory rate (hours) [Time-to event]	The time from first dose of study drug until the time to return to pre-RSV disease level. The return to pre-RSV disease level occurs when the observed value of the parameter is indicated by the investigator as normal, and no later observed values are indicated by the investigator as abnormal (=event). Normalization of respiratory rate (RR) will be derived from the answer to the corresponding question in the questionnaire "is this Respiratory Rate value normal for this patient?" If no deterioration from pre-RSV disease levels occurred, the time will be set to time of first dose of study drug and the value will be set to 0 hours. Subjects with an abnormal value at the last assessment will be censored at that time. Subjects for which this last assessment is the baseline assessment will be censored at time 0.

Measurement	**Formula**
	(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
Time to return to pre-RSV disease level for heart rate (hours) [Time-to event]	Idem as Time to return to pre-RSV disease level for respiratory rate (hours) but for heart rate. Normalization of heart rate (HR) will be derived from the answer to the corresponding question in the questionnaire "is this Pulse value normal for this patient?"
Time to clinical stability (hours) [Time-to event]	The time from first dose of study drug until the time at which the each of the following criteria are met (=event): • Normalization of Oxygen supplementation (as in parameter Time to end of Oxygen supplementation), • Normalization of feeding/hydration (as in parameter Time to end of supplemental feeding/hydration) , • Normalization of respiratory rate (as in parameter Time to return to pre-RSV disease level for respiratory rate), and • Normalization of heart rate (as in parameter Time to return to pre-RSV disease level for heart rate). In case any of the four components is censored, the time to clinical stability will also be censored at the first time-point of the censored component. Subjects who complete or withdraw from the study prior to the event will be censored at the date of completion or withdrawal. If the time is not available they will be censored at 12:00. In case of death the subject will be censored at the maximum observed number of hours until the occurrence of the event or censoring for all subjects achieving the event or being censored because of study completion or withdrawal. (maximum(Date and time of event criteria or censoring) - date and time of first dose of study drug)/3600, rounded to one decimal
Time to return to pre-RSV disease level for body temperature (hours), [Time-to event]	The time from first dose of study drug until the time to return to pre-RSV disease level. The return to pre-RSV disease level occurs when the observed value of the parameter is within the normal range (=event). If no deterioration from pre-RSV disease levels occurred, the

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>time will be set to time of first dose of study drug and the value will be set to 0 hours.

Subjects with an abnormal value at the last assessment will be censored at that time. Subjects for which this last assessment is the baseline assessment will be censored at time 0.

(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal.

The normal ranges can be found in the table below:

<table><tr><th>Measurement method</th><th>Normal temperature range</th></tr><tr><td>Rectal</td><td>36.6°C to 38°C (97.9°F to 100.4°F)</td></tr><tr><td>Ear</td><td>35.8°C to 38°C (96.4°F to 100.4°F)</td></tr><tr><td>Oral</td><td>35.5°C to 37.5°C (95.9°F to 99.5°F)</td></tr><tr><td>Axillary</td><td>34.7°C to 37.3°C (94.5°F to 99.1°F)</td></tr></table></td></tr>
<tr><td>Time to $SpO_2 \geq 93\%$ on room air (hours) [Time-to event]</td><td>The time from first dose of study drug until the time of first SpO_2 measurement $\geq 93\%$ on room air, and where no supplemental oxygen supplementation is given at or after this time point and where no value < 93% are measured after this time point.

Subjects with $SpO_2<93\%$ on room air or who are still on oxygen supplementation at the last SpO_2 assessment will be censored at the date and time of the last SpO_2 assessment.

If no oxygen supplementation was necessary post-baseline and the subject had SpO_2 measurement $\geq 93\%$ on room air at baseline and all post baseline measurements, the value will be set to 0.

(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal</td></tr>
<tr><td>Incidence of acute otitis media</td><td>Did the subject have acute otitis media after first dose of study drug (use high-level term “Middle ear infections and</td></tr>
</table>

Measurement	Formula
	inflammations")? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that didn't have acute otitis media before first dose of study drug.
Incidence of all-cause mortality	Did the subject die after first dose of study drug? Categories will be Yes (1) or No (0).

5.3.2. Analysis Methods

Descriptive statistics

The descriptive statistics that will be shown will include the number of subjects, mean, standard deviation, standard error, 95% confidence interval, median, range and interquartile range.

Time-to event variables

All Time-to event variables will be analyzed using Kaplan-Meier estimates analysis, A summary table including number of subjects included in the analysis, number of subjects censored, 25th and 75th percentiles and median time-to event, with 95% 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 by treatment.

Accelerated failure time (AFT) model

When indicated time-to event variables will be compared between each active treatment group and placebo using an accelerated failure time (AFT) model. The distribution to be used will be determined based on the goodness of fit using Akaike's information criterion and will be selected from the following parametric families: lognormal, log-logistic, or Weibull. The AFT model will include the fixed, categorical effects for treatment (with placebo as the reference) and stratification factor.

A summary of information from the final AFT model will include parameter estimates and associated standard errors, estimated accelerated failure time ratios versus placebo and associated 95% confidence intervals, and p-values. The survival curves per treatment group of the accelerated failure time model will also be shown.

Logistic regression model

A stratified logistic regression model will be used to analyze the binary outcome, with treatment group and stratification factors as fixed effect, will be used to obtain the odds ratios (95% CI) for each comparison versus placebo.

The odds ratios including 95% confidence interval of active groups versus placebo will be derived from the final model using appropriate contrasts. Exact logistic regression models will be used in case the incidence of the events is low (< 10 events).

Model building procedure

In the statistical models following predictive covariates and or baseline indicators may be included: baseline log_{10} viral load, smoking in the environment (yes/no), presence/absence of comorbid diseases, presence/absence of comorbid diseases associated with risk for lower respiratory tract disease, presence/absence of other conditions/therapy of potential interest, days since symptom initiation, RSV subtype, use of corticosteroids, supplemental oxygen at baseline, absence/presence of other viral or bacterial infections and age as continuous variable.

Stepwise forward selection will be used to identify the prognostic factors in combination with backward elimination. A significance value of 0.05 is required for a variable to enter the model and a significance value of 0.10 is required to stay in the model.

5.3.2.1. RSV RNA log_{10} viral load qRT-PCR

Log_{10} Viral Load

Descriptive statistics and mean (SE) graphs will be shown of the log_{10} viral load actual values and changes from baseline. For exploratory purpose the log_{10} viral load actual values and changes from baseline will also be shown by sampling method (measured in the mid-turbinate nasal swabs and endotracheal samples from intubated subjects).

Differences on RSV RNA log_{10} viral load by qRT PCR between treatment groups and by analysis visit will be determined by using appropriate contrasts in the mixed model in which the primary endpoint is modelled. Nominal 95% confidence intervals will be used.

Peak viral load; Rate of decline

The Rate of decline of viral load over the first 24 hours will be analyzed using descriptive statistics including the geometric mean and the coefficient of variation (CV).

The log peak viral load and rate of decline of RSV RNA viral load will be compared for active groups versus placebo groups using a general linear model with treatment and strata included as fixed effects.

Residuals of the final model will be plotted in a normal probability plot.

In case the model does not fit the log peak value data well, the log transformation (ie. the log of log peak viral load) will be considered as dependent variable. The data from the model will be reported as (adjusted) differences in least squares (LS) means (in the case of untransformed data) or (adjusted) geometric mean ratios (in case of log-transformed data) of active dose groups versus placebo, including 95% confidence intervals using appropriate contrasts.

RSV viral load AUC's.

The same model used for the primary analysis will be used to test for a dose response relationship on the viral load AUC until Day 10, until Day 14 and until 1 day after last dose for subjects with treatment extension (if applicable) (respectively $AUC_{1\text{-}10Days}$, $AUC_{1\text{-}14Days}$ and $AUC_{1\text{-}xxDays}$). No corrections for multiplicity will be made, thus the significance level of alpha (α*) will be kept at 0.05. The differences in these AUCs for active versus placebo will be derived using appropriate contrasts deriving least square mean differences, including the 95% 2 sided confidence intervals.

The sensitivity analysis will be similar as for the primary endpoint, using the calculated viral load AUCs per subject based on the trapezoidal method ($AUC_{0\text{-}240h}$, $AUC_{0\text{-}336h}$ and $AUC_{0\text{-}xxh}$) as indicated in section 5.3.1.1.

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 per analysis time point (with corresponding 95% CI), per treatment group and per phase (treatment, follow-up and combined treatment + follow-up).

Subjects with missing data on that analysis visit will not be counted in the denominator for the proportion.

In addition, a stratified logistic regression model will be used to analyze the outcome.

Time to peak viral load

This time-to event variable will be analyzed as indicated above using Kaplan-Meier analysis.

Time to virus undetectable [time-to event]

This time-to event variable will be analyzed as indicated above using Kaplan-Meier analysis.

Additionally, the time-to event data will be analyzed using the logrank test and Gehan-Wilcoxon method.

Time to virus undetectable [interval censored]

The differences in time to RSV RNA being undetectable of active dosing regimens versus placebo treatment will also be estimated using the accelerated failure time model based on interval censored data. Treatment and stratum will be added as fixed categorical effects, while log baseline viral load will be added as a continuous fixed covariate.

Treatment effect versus placebo will be reported as an acceleration factor including 95% confidence intervals for each active treatment group. Estimated survival curves will be created based on the mean baseline viral load value and weighted average for each stratum.

The baseline log_{10} viral load will be included as the continuous covariate. Other covariates and or baseline indicators may be included in the model when of predictive value. The model building procedure will be used.

5.3.2.2. RSV RNA log_{10} viral load plaque assay (exploratory endpoints)

As exploratory analysis, the viral load measured using a quantitative viral culture (plaque assay) will be analyzed with descriptive statistics and mean (SE) graphs for both the actual values and changes from baseline. Additionally this analysis will be done by swab method (measured in the mid-turbinate nasal swabs and endotracheal samples from intubated subjects).

5.3.2.3. RSV clinical outcome

Length of hospital stay and time to readiness for discharge.

These time-to event variables will be analyzed as indicated above using Kaplan-Meier analysis, and will also be compared between each active treatment group and placebo using an accelerated failure time (AFT) model. .

Additionally, the time-to event data will be analyzed using the logrank test and Gehan-Wilcoxon method comparing each active treatment to placebo

Duration of intensive care unit (ICU) stay (hours) [Duration]

The duration in the ICU will be analyzed descriptively for all subjects and by subgroup of subjects staying / not staying in the ICU at the time of first dose of study drug.

Requirement for intensive care or supplemental support

The requirement for intensive care unit (ICU) stay, for oxygen supplementation, for noninvasive mechanical ventilation support, for invasive mechanical ventilation support, for supplemental feeding/hydration will be analyzed similarly. These requirement parameters will only be calculated for those subjects that don't require intensive care or supplemental support (depending on the parameter of interest) before first dose of study drug.

The proportion of subjects within the requirement categories (yes and no) will be shown in a frequency tabulation (with corresponding 95% CI) and per treatment group.

In addition, a stratified logistic regression model will be used to analyze the outcome

The analyses of the requirement parameters will answer the question:
Is there a treatment difference in preventing the use of intensive care or supplemental support?

Time to end of intensive care or supplemental support

These time-to event parameters will be analyzed for those subjects that require intensive care or supplemental support (depending on the parameter of interest) before first dose of study drug,

Kaplan-Meier analysis and stratified Gehan test to compare active treatment groups versus placebo will be used.

These time-to event parameters will answer the question:
Is there a treatment difference in the time to no longer requiring intensive care or supplemental support?

While we cannot integrate the results on the requirement for intensive care or supplemental support and the time to end of intensive care or supplemental support they are conceptually linked. We will combine the p-values for both independent tests for the comparison of each active group versus placebo using the method of Liptak[3].

Additionally these time-to event parameters will be analyzed for all ITT-i subjects using Kaplan-Meier analysis as indicated above and using a stratified Gehan test to compare between treatment groups

Time to clinical stability and Time to return to pre-RSV disease level

These time-to event parameters will be analyzed as indicated above using Kaplan-Meier analysis.

The differences in time of active dose regimens versus placebo treatment will be estimated using a Cox proportional hazard model; as baseline covariates, stratification factors, absence/presence of other viral or bacterial infections, and baseline $\log_{10}$ viral load will be added. Treatment effect versus placebo will be reported, including 95% confidence intervals. A Log-log plot of survival will be added to check the proportional hazard assumption.

Additionally, the time-to event data will be analyzed using the logrank test and Gehan-Wilcoxon method.

Incidence of acute otitis media and all-cause mortality

The incidence of acute otitis media and of all-cause mortality will be analyzed similarly. Note that these incidences are only analyzed if any subjects have acute otitis media or if any deaths occur.

The proportion of subjects with presence/absence of acute otitis media and who died yes/no will be shown in a frequency tabulation (with corresponding 95% CI) and per treatment group.

A stratified logistic regression model will be used to analyze the outcome.

Relationship between RSV RNA viral load and clinical outcome

The following relationships will be investigated:

RSV RNA $\log_{10}$ viral load $AUC_{0\text{-}144h}$ versus

- Requirement for oxygen supplementation
- Time to end of Oxygen supplementation

- Length of hospital stay
- Time to readiness for discharge
- Length of hospital stay since hospital admission
- Time to readiness for discharge since hospital admission
- Time to clinical stability
- Time to return to pre-RSV functional status

The definitions of these parameters can be found in sections 5.3.1.

A Tabulation of the requirement for oxygen supplementation will be presented by quartiles of viral load $AUC_{0\text{-}144h}$.

Kaplan-Meier analysis by quartiles of viral load $AUC_{0\text{-}144h}$ will be done for the time to variables.

Relationship between RSV RNA viral load and signs and symptoms of RSV infection

The following relationships will be investigated:

Quartiles of viral load $AUC_{0\text{-}144h}$ versus

- Severity of signs and symptoms of RSV infection as rated by the clinician.

The relationships described above will de explores by using the spearman's rank correlation coefficients and scatterplots with smoother curve per treatment group.
The definitions of these parameters can be found in sections 5.3.2.1 and 5.4.1.

5.4. Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS)

5.4.1. Definition

Currently, no single outcome assessment tool is widely accepted to assess the severity of RSV in infants and children. Although various clinical scores have been developed for the evaluation of the severity of acute respiratory infections and/or bronchiolitis in infants and children, none have been sufficiently validated for the longitudinal monitoring of the severity of RSV infection. Considering that there are no widely accepted or fully validated clinical endpoints for use in studies of RSV treatment, the PRESORS, an electronic clinician and parent/caregiver RSV infection severity rating assessment, will be further developed and evaluated for validity and reliability in a phase 0 trials, 64041575RSV0001.

The PRESORS data may also be analyzed for specific psychometric properties outside the scope of this protocol (possibly in conjunction with data from study 64041575RSV0001). In that case results will also be reported separately.

This study includes the same version of the PRESORS as in this validation study. The scoring system that will be used during this validation is available in attachment 4.
The PRESORS scores are defined as in table below. These will be calculated at each scheduled time point a questionnaire was filled in. A change from baseline will also be calculated.

Domain	Items	Scoring
Severity of signs and symptoms during the past 12 hours as assessed by the Clinician	Attachment 4: Items 1-5 (Clinician)	Sum of the individual item scores. See appendix for item score.
Severity of signs and symptoms now as assessed by the Clinician	Attachment 4: Items 6-14 (Clinician)	Sum of the individual item score. See appendix for item score.
Study drug administration as assessed by the Clinician	Clinician's Items: Study drug administration	Number of reports, ranging from 0 (no reports) to 6.
Severity of signs and symptoms as assessed by the Caregiver	Attachment 4: Items 1-12 (Caregiver)	Sum of the individual item score. See appendix for item score.
Breaths/minute	Caregiver: Breaths/15s	4 times the Breaths per 15 seconds
Improvement during the past 12 hours as assessed by the Clinician	Attachment 4: Items 1-5 (Clinician)	Number of signs and symptoms that have decreased by at least 2 points during the past 12 hours as assessed by the Clinician per time point.
Improvement now as assessed by the Clinician	Attachment 4: Items 6-14 (Clinician)	Number of signs and symptoms that have decreased by at least 2 points now as assessed by the Clinician per time point.

Improvement as assessed by the Caregiver	Attachment 4: Items 1-12 (Caregiver)	Number of signs and symptoms that have decreased by at least 2 points as assessed by the Caregiver per time point.

5.4.2. Analysis Methods

Frequency tabulations of each of the individual items at baseline, day 7, 14 and 28.

Severity and Improvement of Signs and Symptoms of the RSV infection

Actual values and changes from baseline will be summarized by treatment group at each scheduled time point for the PRESORS scores (severity), child's temperature, breaths per minute, time spent with the child and hours missed from usual activities.

Mean±SE graphs over time for the actual values and changes from reference will be presented.

Analyses of the PRESORS scores may be performed to further investigate validity of this instrument. These will be described outside this SAP and, if performed, will be reported outside the CSR.

Duration of Signs and Symptoms of the RSV infection

See secondary endpoint: Time to readiness for discharge.

Relationship between viral load and duration of signs and symptoms of RSV symptoms as assessed by the PRESORS questionnaire completed by the clinician

Kaplan-Meier analysis by quartiles of viral load $AUC_{0\text{-}7\ days}$ for the duration of signs and symptoms of RSV symptoms

A summary table including number of subjects included in the analysis, number of subjects censored, 25th and 75th percentiles and median with 95% confidence intervals based on log-log transformation method, will be presented by quartiles of viral load AUC0-7 days parameter.

The relationship between the clinician eCOA and parent(s)/caregiver(s) eCOA responses

The relationship between the severity of signs and symptoms as assessed by the clinician and the parent(s)/caregiver(s) will be assessed using spearman rank correlation between the clinician's score (both during the past 12 hours and now) and the parent(s)/caregiver(s) score. This correlation will be evaluated at baseline and on all scheduled assessments where both the clinician eCOA and caregiver eCOA have been performed. Other methods may be considered as appropriate.

6. SAFETY

All safety analyses will be done on the Safety Set.

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):

- In case of partial start or stop dates, the events are allocated to the phases using the available partial information on start and end date; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the phases. This rule may lead to multiplication of the event as a consequence of its assignment to multiple phases.

- In case of a completely missing start date, the event is allocated to the first active treatment phase, except if the end date of the AE falls before the start of the first active treatment phase.

- In case of a completely missing end date, the following decision rules apply:

  - in case the date is identified as unknown the date will remain missing;

  - in case the date is not flagged as unknown the date is imputed by the cut-off date of the analysis for subjects still ongoing in the study, and by the end date of the last phase for subjects who discontinue.

Examples:

Screening phase: start date: 02JAN2017 - stop date: 28JAN2017
Treatment phase: start date: 29JAN2017 - stop date: 12AUG2017

1) Adverse event: start date: JAN2017- stop date: 15JUL2017
   As the start date only has information about month and year, only this information will be used from the phases and therefore the AE will be assigned to the screening phase as well as to the treatment phase.

2) Adverse event: start date: JAN2017- stop date 27JAN2017 As the AE stops before or at the start of the treatment phase, it is only assigned to the Screening phase.

Remarks:

In addition to the date information, time information is taken into account to allocate AEs to phases.

6.1.2. Analysis Methods

A summary will be provided for the following emergent adverse events per phase (Treatment phase, Follow-up phase) and for the combination of Treatment and Follow-up phase:

- 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,
- serious adverse events that were at least possibly related to study medication.

There will be no formal statistical testing.

Incidence tabulations will be provided for individual adverse events in the above categories (in case there are at least 5 events).

Listings will be provided for at least the following categories: all AEs, serious AEs, AEs leading to death, AEs leading to permanent stop, grade 3-5 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) by subgroups (section 2.4): any AE, any RSV-related complications, any grade 3-5 AE, AEs that are at least possibly related to study medication, AEs leading to death, serious AEs, AEs leading to permanent stop of study medication.

6.2. Clinical Laboratory Tests

Laboratory parameters of hematology, serum chemistry and urinalysis will be investigated: All analyses will be done on SI-converted values as available in the database.

6.2.1. Definitions

Unifying multiple laboratory values by standardization:

Since local labs are used, the SI-converted values will be harmonized for selected parameters using the following formula and using the phantom laboratory generalized lab norms (GLN) as proposed by Francis Ruvuna, David Flores *et al*.[4]

$$y = (x - L_i) * \frac{U_{cs} - L_{cs}}{U_i - L_i} + L_{cs}$$

Where

y	=	the transformed individual analyte value to a common standard laboratory reference range;
x	=	the original value;
L_i and U_i	=	lower and upper limits of normal for individual laboratory analyte;
L_{cs} and U_{cs}	=	lower and upper limit for the selected common standard laboratory or phantom laboratory GLN

The following additional rule applies for standard normal ranges with zero as lower limit and local normal ranges with non-zero lower limit. Zero will be used as lower local limit in the formula if the previous mentioned requirement was met.

The harmonized values, with the phantom laboratory GLN, will be used during the analysis.

Toxicity grades and abnormalities for laboratory parameters:

Toxicity grades will be computed according to the DMID adult toxicity grading list (see attachment at the end of this document) based on the harmonized values, for the parameters with harmonized values. In case different grades are available for fasted/non fasted results, the results are assumed to be taken in the condition as specified in the protocol (i.e. not necessarily according to possible remarks indicating a deviation to this). If no condition is specified in the protocol, the non-fasting gradings should be used.

In case no toxicity grades are defined for any laboratory test, then non-graded abnormalities (high/low vs. normal range) will be used instead.

The worst grade over the whole observational period (treatment phase, follow-up phase and combination of treatment and follow-up) will be determined.

Emergent definition for toxicity grades and abnormalities

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered emergent in a particular phase if it is worse than the baseline value. If the 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 emergent definition is applicable in both, the treatment and follow-up phase.

In case of missing date or time parts

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 data base 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.

6.2.2. Analysis Methods

Actual values and change from baseline will be summarized by treatment group at each scheduled time point.

A cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (Treatment phase, Follow-up phase) and for the combination of 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 and the cumulative number of subjects per emergent toxicity/abnormality or worse.

Mean±SE graphs over time for the actual values and changes from reference will be generated for all tests performed.

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, and will include both the original and harmonized values.

Grade 2 or higher toxicity laboratory values will be listed separately.

Urinalysis results will be listed. Proteinuria and urine WBCs will be summarized.

6.3. Vital Signs

Systolic and Diastolic blood pressure, heart rate, respiratory rate, body temperature and oxygen saturation (SpO_2) will be investigated.

6.3.1. Definitions

The vital signs abnormalities will be defined as indicated in Attachment 2. In determining the abnormalities, the following rules are applied:

- worst grades/abnormalities are determined over the whole observational 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%)

An abnormality will be considered emergent in a particular phase 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.

Note: As described in section 2.1, for vital signs, means per analysis timepoint window will be calculated in order to have 1 assessment per analysis timepoint. These mean values per analysis timepoint will be used in the descriptive analyses over time. Abnormalities, to be used in the determination of the worst abnormality per phase, will not be determined on these mean values, but on the original records, including both scheduled and unscheduled assessments.

6.3.2. Analysis Methods

Actual values and change from baseline will be summarized by treatment group at each scheduled time point.

A cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (Treatment phase, Follow-up phase) and for the combination of 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 and the cumulative number of subjects per emergent toxicity/abnormality or worse.

Mean±SE graphs over time for the actual values and changes from baseline will be generated for all tests performed.

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

6.4. Physical Examination Findings

Abnormal physical examination will be listed.

6.5. Electrocardiogram

PR, QT, QRS, QTc intervals and heart rate will be investigated. QTcF values will be used as reported, they will not be recalculated.

6.5.1. Definitions

The ECG abnormalities will be defined as indicated in Attachment 3. In determining the abnormalities, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period and 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%)

An abnormality will be considered emergent in a particular phase 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’ or ‘grade …’ post baseline (or vice versa) is also emergent.

6.5.2. Analysis Methods

Actual values and change from baseline will be summarized by treatment group at each scheduled time point.

A cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (Treatment phase, Follow-up phase) and for the combination of 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 and the cumulative number of subjects per emergent toxicity/abnormality or worse.

A tabulation of the worst QT/QTc change versus baseline per treatment per phase (Treatment phase, Follow-up phase) and for the combination of Treatment and follow-up phase will be presented

Mean ± SE graphs over time for the actual values and changes from baseline will be generated for all tests performed.

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

7. VIROLOGY

7.1. Viral Strain Typing

The RSV subtype is determined at baseline using the RSV-A/B qRT-PCR assay performed at the central lab.

7.2. Viral Sequencing

Viral resistance will be evaluated by next-generation sequencing (NGS) of the RSV polymerase L-gene Baseline samples from all subjects will be sequenced to identify pre-existing polymorphisms in their L gene. Post-baseline sequencing will be performed on the last evaluable on-treatment sample for all subjects to identify emerging amino acid substitutions in the L gene. Additional post-baseline sequencing can be performed on request of the sponsor virologist. Further validation of the RSV L-gene next generation sequencing assay is currently ongoing to determine the read frequency cut-off that will be used in the analyses.

7.2.1. Definitions

Virology results will be assigned to the visit windows as described in section 2.1 Visit Windows and Phase Definition. In addition to the time points corresponding to the visits at which samples for RSV L-gene sequencing are collected, the below time points will be considered:

- Baseline (BL): Time point with sequencing data available closest and prior to the first dose (ie the loading dose).
- Sequence at End of Treatment (EOTSTPT): Last available post-baseline time point during the treatment phase with sequencing data available
- Sequence at End of Study (EOSSTPT): Last available post-baseline time point in the study with sequencing data available
- Entire post-baseline phase: Aggregate of all available post-baseline time points in the study with sequencing data available

Genetic variations are defined as changes (on amino acid or nucleotide level) in the subject's virus's 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 polymorphism:** amino acid difference from the RSV-A or RSV-B reference strain detected at baseline above a certain read frequency cut-off.
- **Emerging genetic variation:** a genetic variation (amino acid substitution, insertion or deletion) that is absent (ie below the NGS read frequency cut-off) at baseline but present above a certain read frequency cut-off at a later post-baseline time point.

- **Enriched genetic variation**: a genetic variation (amino acid substitution, insertion or deletion) that is present at baseline and detected post-baseline with a minimum increase in read frequency compared to baseline.

- **Genetic variation profile**: a specific genetic variation or combination of genetic variations at one or more time points

- **RSV L-gene amino acid positions of interest**: The 4 L-gene positions of interest are 628, 789, 795 and 796 (based on in vitro selection experiments with Lumicitabine)

The read frequency cut-off that will be used for reporting RSV L-gene NGS data, as well as the read frequency cut-offs used in the definitions of baseline polymorphisms, emerging and enriched genetic variations are not yet defined but will be prior to the start of the analyses.

7.3. Analysis Methods

Baseline

The prevalence of baseline polymorphisms in the RSV L-gene, ie the number of subjects with baseline polymorphisms in the RSV L-gene, will be tabulated in frequency tabulation (n, %) by analysis time point and for the entire post-baseline phase. Amino acid changes from reference sequence at baseline will be listed for all subjects using the read frequency cut-off of the RSV L-gene NGS assay. Additionally frequency tabulations per time point and for the entire post-baseline phase will be made selecting only those baseline polymorphisms above a certain read frequency.

Similar tabulations will be made for the baseline polymorphisms on the positions of interest.

Post-baseline

Emerging and enriched genetic variations will be tabulated by analysis time point and for the entire post-baseline phase in frequency tabulations (n, %). Amino acid changes from reference sequence will be listed for all subjects with post-baseline sequencing data using the read frequency cut-off of the RSV L-gene NGS assay. Additionally frequency tabulations per time point and for the entire post-baseline phase will be made selecting only those emerging and enriched genetic variations above a certain read frequency.

Similar tabulations will be made for the emerging and enriched genetic variations on the positions of interest.

8. HEALTH ECONOMICS

Following medical resource utilization data will be explored.

8.1. Definitions

Measurement	**Formula**
Number of medical care encounters	Medical care encounters, including surgeries and other selected procedures (inpatient and outpatient), as recorded on the eCRF. The number of medical care encounters is derived as the frequency of the medical encounters other than those mandated in the protocol (eCRF).
Number of outpatient medical care encounters	Similar to the description for number of medical care encounters, but only for outpatient medical care encounters, as recorded on the eCRF (Hospital Outpatient Department, Laboratory Department, Medical Practitioner Office, Home Care).
Duration of medical care encounter (days) per medical care encounter	Duration of medical care encounter, is defined per medical encounter. (End date of last medical care encounter – start date of first medical care encounter)+1.
Requirement for hospital readmission for respiratory reasons	Does the subject require hospital readmission (ER, ICU, Hospice/Palliative Care Unit, Hospital Inpatient Department) for respiratory reasons after discharge? Categories will be Yes (1) or No (0). Only derive this parameter for subjects that were discharged from hospital after first dose of study drug.
Requirement for hospital readmission for any reasons	Similar as Requirement for hospital readmission for respiratory reasons
Duration of hospital readmission for respiratory reasons	Duration of hospital readmission for respiratory reasons from discharge until end of the trial. The duration of the readmissions can be calculated based on the start and end date of these medical readmissions. If more than 1 readmission took place, the duration can be calculated as the sum of the different durations.
Duration of hospital readmission for any	Similar as Duration of hospital readmission for respiratory reasons

reason	
Hospital readmission for respiratory reasons	Medical review will be done immediately before data base lock on a list with unique coded adverse events (MedDRA Preferred Terms) for subjects who are re-admitted to the hospital to indicate which subjects were re-admitted for respiratory reasons

8.2. Analysis Methods

Descriptive statistics or frequency tabulations will be presented for all above parameters (except for the durations parameters) by treatment group.

A patient listing with details on the individual medical encounters will be created.

REFERENCES

1. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate in children from birth to 18 years: a systematic review of observational studies. Lancet. 2011;377(9770):1011–1018.
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3. Liptak, T. (1958). "On the combination of independent tests". Magyar Tud. Akad. Mat. Kutato Int. Kozl. 3: 171–197.
4. 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

ATTACHMENT 1. : LABORATORY: 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	-	20-25 mg/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)

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

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

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 - 11.2 mg/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 - 11.2 mg/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)

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

ATTACHMENT 2. : VITAL SIGNS

The following classes for vital signs abnormalities will be defined based on the references [1] and [2], and internal pediatrician insight at J&J:

Parameter (unit)	Abnormality class	Age class				
		0 - 3 months	3 - 6 months	6 - 12 months	1 - 2-years	2- <3 years
Diastolic BP (mmHg)	abnormally low clinically relevant	<35	<40	<40	<40	<40
	abnormally low not clinically relevant	35 - <45	40 - <50	40 - <55	40 - <55	40 - <45
	Normal	45 - 55	50 - 65	55 - 65	55 - 70	45 - 60
	abnormally high not clinically relevant	>55 - 65	>65 - 85	>65 - 85	>70 - 90	>60 - 70
	abnormally high clinically relevant	>65	>85	>85	>90	>70
Systolic BP (mmHg)	abnormally low clinically relevant	<60	<60	<60	<75	<80
	abnormally low not clinically relevant	60 - <65	60 - <70	60 - <80	75 - <90	80 - <85
	Normal	65 -85	70 - 80	80 - 100	90 - 105	85 - 100
	abnormally high not clinically relevant	>85 - 110	>80 - 110	>100 - 110	>105 - 120	>100 - 110
	abnormally high clinically relevant	>110	>110	>110	>120	>110
Heart rate HR (bpm)	abnormally low clinically relevant	<80	<70	<70	<60	<90
	abnormally low not clinically relevant	80 - <100	70 - <90	70 - <80	60 - <70	90 - <95
	Normal	100 - 150	90 - 120	80 - 120	70 - 110	95 - 125
	abnormally high not clinically relevant	>150 - 180	>120 - 150	>120 - 150	>110 - 140	>125 - 130
	abnormally high clinically relevant	>180	>150	>150	>140	>130
Respiratory rate	abnormally low clinically relevant	<25	<20	<20	<18	<20
	abnormally low not clinically relevant	25 - <35	20 - <30	20 - <25	18 - <20	20 - <22
	Normal	35 - 55	30 - 45	25 - 40	20 - 30	22 - 30
	abnormally high not clinically relevant	>55 - 70	>45 - 60	>40 - 60	>30 - 50	>30 - 35
	abnormally high clinically relevant	>70	>60	>60	>50	>35
Oxygen saturation SpO_2 (%)	abnormally low clinically relevant	<92	<92	<92	<92	<92
	abnormally low not	92 - <96	92 - <96	92 - <96	92 - <96	92 - <96

Parameter	**Abnormality class**	**Age class**				
	clinically relevant					
	Normal	≥96	≥96	≥96	≥96	≥96

ATTACHMENT 3. : ECG

The following classes for ECG abnormalities will be defined:

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	0 - 2 years	NA	>150
	2 - <3 years	<100	>150
QRS (msec)	0 - 2 years	NA	>79
	2 - <3 years	<40	>79
QT (msec) and QTc (msec)	0 - 2 years	NA	>500
	2 - <18 years	<320	>450
RR (msec)	0 - 3 months	<333	>750
	3 - 12 months	<400	>860
	1 - 2 years	<430	>1000
	2 - <18 years	<600	>1200

Criteria for Abnormal QTc Changes From Baseline		
	Classification	
QTc change from baseline	No concern	≤30
	Concern	>30 – ≤60
	Clear concern	> 60
These criteria are based on the ICH E14 Guideline		

ATTACHMENT 4. : PRESORS – INVESTIGATORS – SUBJECT'S STATUS DURING THE PAST 12 HOURS

Symptoms

	Item	0 points	1 point	2 points	3 points
1	Activity level	Alert and active/normal sleep	Irritable/restless /agitated	Floppy/lethargic/poor interaction	Only responds to pain/unresponsive
2	Sleep	Normal	Occasional restlessness/disturbed	Restless/disturbed much of time	Comatose
3.1	Breathing problems: retractions	No retractions	Subcostal retraction	Intercostal retraction	Tracheosternal retraction
3.2	Breathing problems: other signs	No signs of increased work of breathing (excluding retractions)	Nasal flaring OR grunting OR other signs of increased work of breathing (excluding retractions)	Head bobbing or 2 out of 3 from nasal flaring, grunting, or other signs of increased work of breathing (excluding retractions)	Head bobbing and at least one out of 3 (or 3 out of 3 without head bobbing) from nasal flaring, grunting, or other signs of increased work of breathing (excluding retractions)
4.1	Cyanosis	Absent			Present
4.2	Apnea	Absent			Present
4.3	General	No signs	Cough or nasal secretions	Wheezing and/or both cough and nasal secretions	
5	Feeding	>75% of normal amount of feeds via usual route	50% to 75% of normal amounts of feeds via usual route	< 50% of normal feeds or needing NG feeds or IV fluids	

PRESORS – Investigators – subject's status now

Symptoms

	Item	0 points	1 point	2 points	3 points
6	Activity level	Alert and active/normal sleep	Irritable/restless /agitated	Floppy/lethargic/poor interaction	Only responds to pain/unresponsive
7.1	Breathing problems: retractions	No retractions	Subcostal retraction	Intercostal retraction	Tracheosternal retraction
7.2	Breathing problems: other signs	No signs of increased work of breathing (excluding retractions)	Nasal flaring OR grunting OR other signs of increased work of breathing (excluding retractions)	Head bobbing OR 2 out of 3 from nasal flaring, grunting, or other signs of increased work of breathing (excluding retractions)	Head bobbing AND at least one out of 3 (or 3 out of 3 without head bobbing) from nasal flaring, grunting, or other signs of increased work of breathing (excluding retractions)
8	Cyanosis	Absent			Present
9	Coughing	Little or no coughing	Occasional strong cough, sometimes productive	Frequent cough, sometimes causing choking, gagging, or vomiting	
10	Nasal Secretion	Minimal, easily cleared with suctioning	Moderate, but could be cleared with suctioning	Extensive, requires frequent suctioning	
11	Wheezing	No wheezing	Terminal expiratory wheezing or only with stethoscope	Entire expiration or audible during expiration without stethoscope	Inspiration and expiration without stethoscope
12	Dehydrated	Absent			Present
13	General Condition 1	No concerns (condition is stable or improving)		Some concerns (may become unstable/requires close observation)	Extremely concerned (unstable, requires immediate medical review)
14	General Condition 2	Excellent	Good	Fair	Poor

PRESORS – Caregiver

Recall period:
Screening an baseline: "over last 12 hours"
Post baseline through Day 14: "Since bedtime last night", "Since the child woke up this morning"
Day 14 through Day 27: "Since this time yesterday"
Day 28: "Over the last 24 hours"

Symptoms

	Item	0 points	1 point	2 points	3 points
1	General condition	Excellent	Good	Fair	Poor
2	Activity level	As active as usual	A little less active than usual	A lot less active than usual	Floppy or limp, not responding to you as usual
3	Sleep	Slept about as much as usual	Slept a little less/more than usual	Slept a lot less than usual	Slept a lot more than usual
4	Crying	Normal, no more crying than usual	Cried more than usual but calmed if held or soothed	Cried a lot, difficult to calm even if held or soothed	Cried a lot, would not stop crying even if held or soothed
5	Wheezing	None	Yes, but only at the end of when the child breathes out	Yes, throughout breathing out	Yes, through breathing in and out
6.1	Breathing problems	None	Skin between the ribs sucked in when breathing in	Skin at the base of the throat sucked in when breathing in	Belly sucked in when breathing in
6.2	Breathing problems	None	Unable to breathe through stuffy or runny nose OR breathing faster than usual OR nostril flared out when breathing in OR made grunting sounds when breathing	Head bobbed up and down when breathing OR two of: unable to breathe through stuffy or runny nose / breathing faster than usual / nostril flared out when breathing in / made grunting sounds when breathing	Gasping for air/long pauses between breaths OR head bobbed up and down when breathing AND one from unable to breathe through stuffy or runny nose / breathing faster than usual / nostril flared out when breathing in / made grunting sounds when breathing OR ≥3 from those
7	Cyanosis (lips, skin, fingernails pale or blue)	Absent		Present, but only when the child was crying	Present, even when the child has not been crying
8	Cough	None	A little coughing	Coughing a lot	Coughing almost all the time
9	Vomit	None	Yes, only when coughing	Yes	
10	Feeding	Yes, drank/nursed as usual	No, drank/nursed a little less than usual	No, drank/nurse a lot less than usual	No, did not drink or nurse at all
11	Urination	Yes, as usual	No, a little less than usual	No, a lot less than usual	No, did not wet a diaper or use the toilet

12	Dehydration	None	Dry skin or lips OR sunken frontal fontanelle OR sunken soft spot on top of the head OR sunken eyes OR dark yellow urine	Two signs from: dry skin or lips / sunken frontal fontanelle / sunken soft spot on top of the head / sunken eyes/ dark yellow urine	Three or more signs from: dry skin or lips / sunken frontal fontanelle / sunken soft spot on top of the head / sunken eyes/ dark yellow urine