Janssen Research & Development

Statistical Analysis Plan

A Phase 2b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of Orally Administered ALS-008176 Regimens in Adult Subjects Hospitalized with Respiratory Syncytial Virus

Protocol 64041575RSV2003; Phase 2b

ALS-008176 (JNJ-64041575)

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

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AMENDMENT HISTORY

Not applicable

ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
ANCOVA	Analysis of Covariance
AST	Safety Set or All Subjects Treated
AUC	Area Under the Curve
BMI	Body Mass Index
CAD	Coronary Heart Disease
CI	Confidence Interval
CPAP	Clinical Pharmacology Analysis Plan
CRF	Case Report Form
CRF	Chronic Renal Failure
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eCOA	electronic Clinical Outcome Assessment
FDA	Food and Drug Administration
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
ITT	Intention-to-Treat
ITT-i	Intention-to-Treat-infected
IWRS	Interactive Web Response System
LD	Loading Dose
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MD	Maintenance Dose
OBF	O'Brien-Fleming
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
qRT-PCR	Quantitative real-time Reverse Transcriptase-polymerase chain reaction
RAND	Randomized Analysis
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT	Randomized or Treated
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the analysis of efficacy and safety of the investigational compound ALS-008176 (also known as JNJ-64041575). 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).

ALS-008176 is a 3',5'-bisisobutyrate prodrug, which is readily metabolized to the cytidine nucleoside analog, ALS-008112. Subsequently, inside cells, ALS-008112 is efficiently converted to its nucleoside triphosphate, ALS-008136. This nucleoside triphosphate is a potent inhibitor of respiratory syncytial virus (RSV) ribonucleic acid (RNA)-dependent RNA polymerase activity and works via a classic chain termination mechanism. ALS-008144, the uridine metabolite of ALS-008112, is the inactive major metabolite noted in systemic circulation.

1.1. Trial Objectives

Primary Objective

The primary objective is to determine in adults who are hospitalized with RSV infection the dose-response relationship of multiple regimens of ALS-008176 on antiviral activity based on nasal RSV shedding using quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) assay.

Secondary Objectives

The secondary objectives are to determine in adults who are hospitalized with RSV infection:

- The impact of ALS-008176 on the clinical course of RSV infection including:
  - Duration of hospital stay.
  - Duration of supplemental oxygen.
  - Evolution of Activities of Daily Living (ADL) as assessed by Katz ADL score.
  - Time to clinical stability.
  - Improvement on the ordinal scale.
  - Rate of mortality and complications.
- The time to cessation of nasal RSV shedding.
- The impact of ALS-008176 on the emergence of resistant strains of RSV.
- The safety and tolerability of ALS-008176.
- The pharmacokinetics (PK) of ALS-008112 and ALS-008144 (and other metabolites, if applicable) in plasma.

- The relationship between the PK and pharmacodynamics (PD; antiviral activity, clinical symptoms, and selected safety parameters) after single (loading dose [LD]) and repeated oral dosing (maintenance dose [MD]) of ALS-008176.

Exploratory Objectives

The exploratory objectives are to evaluate in adults who are hospitalized with RSV infection:

- The relationship between viral kinetics and clinical outcome, including the relationship between RSV RNA viral load and:
  - Oxygen supplementation.
  - Duration of hospitalization.
  - Katz ADL.
  - Clinical stability.
- The impact of the baseline viral subtype and genotype on the antiviral response.
- Onset of complications after initiation of treatment.
- The impact of ALS-008176 on the clinical course of RSV during and following hospitalization as assessed by the subject in the electronic Clinical Outcome Assessment (eCOA) using various scoring systems.
- The impact of RSV and its treatment on health-related quality of life (HRQoL) as assessed by the subject in the eCOA.
- The relationship between the Katz ADL and the subject eCOA responses.
- Medical resource utilization to manage subjects.
- The comparison of the RSV RNA viral loads measured in mid-turbinate nasal swabs and endotracheal samples from intubated subjects.
- To explore the evolution of diffusing capacity of the lung for carbon monoxide (DLCO) and spirometry in subjects hospitalized due to RSV infection.

Additionally, the impact of ALS-008176 on the infectious viral load may be evaluated using a quantitative culture of RSV (plaque assay) on a selected number of subjects and samples.

1.2. Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-grouped, multicenter, dose-finding study of ALS-008176.

A target of approximately 90 subjects, ≥50 years of age who are hospitalized with RSV, will be randomly assigned in this study with 30 subjects planned per treatment regimen.

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

- Regimen A (placebo): a single LD (Dose 1) followed by 9 MDs (Doses 2 to 10) of matching placebo, administered twice daily.

- Regimen B (low-dose ALS-008176): a single 750 mg LD (Dose 1) followed by nine 250 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.
- Regimen C (high-dose ALS-008176): a single 1,000 mg LD (Dose 1) followed by nine 500 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.

The randomization will be balanced by using randomly permuted blocks and will be stratified by region (Japan versus non-Japan) and age (≥50 to <65 years and ≥65 years).

The study will be conducted in 3 phases: a screening phase, a treatment phase from Day 1 to Day 5/6 (depending on the timing of the LD), and a follow-up phase for a total of 28 days post randomization. In the follow-up phase, subjects will have assessments completed at Day 7, Day 10, Day 14, and Day 28. Depending on discharge date, assessments will be completed either while hospitalized or during outpatient visits. For hospitalized subjects additional assessments are done as per the Time and Events Schedule. The duration of the subject's participation will be approximately 28 days, screening period not included.

Screening for eligible subjects will be performed as soon as possible following admission to the emergency room or hospitalization, such that subjects are randomized within 5 days of RSV symptom onset. Men or women ≥50 years of age diagnosed with RSV infection based on a polymerase chain reaction (PCR)-based diagnostic assay (with or without co-infection with another respiratory pathogen) who have been (or will be) admitted to the hospital and who have signed informed consent will be enrolled.

The study drug ALS-008176 will be provided as tablets for oral administration. Study drug administration should start as soon as possible, but no later than 4 hours after randomization in order to maximize the opportunity for the compound to inhibit viral replication and potentially improve outcomes. Subjects will be dosed with a single oral LD followed by 9 MDs twice daily (at least 8 hours apart) during Day 1 to Day 5/6 (depending on the timing of the LD). Administration of the doses should occur at approximately the same time each day after the collection of the mid-turbinate nasal swabs.

Assessments during the study will include the antiviral activity, measured by mid-turbinate nasal RSV RNA viral load using a qRT-PCR assay as well as an evaluation of the clinical course of RSV infection as assessed by the clinician and an evaluation of RSV disease-related signs and symptoms and HRQoL as assessed by the subject.

Safety and tolerability, including AEs, laboratory assessments, ECGs, physical examination, and vital signs will be assessed throughout the study from signing of the informed consent form (ICF) until the subject's last study-related activity.

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

Sequence analysis will be performed to identify pre-existing sequence polymorphisms, to characterize RSV variants of the L-gene and other regions of the RSV genome if warranted, and to evaluate emergence of any resistance-associated mutations. Additionally, exploratory

biomarkers (derived from blood biomarker samples, leftover mid-turbinate nasal specimens, or leftover blood samples) may be assessed to determine the effects of ALS-008176 on markers of RSV disease.

An unblinded IDMC will be commissioned for this study and a Sponsor Committee will be established. Based on the recommendations of the IDMC following interim analyses/reviews of PK, efficacy, and safety data, changes to enrollment in the treatment arms, dose regimen adjustments, or an increase in dose duration to 10 days may be implemented. A maximum of 2 interim analyses are planned to assess the primary endpoint for early superiority and futility. The first interim analysis will be performed when at least 45 subjects have been randomized, preferably after the end of a hemispheric RSV season. If the study is considered underpowered, a sample size increase may be suggested to a maximum of 180 subjects.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis is that there is a positive dose-response relationship of active treatment on the average RSV RNA viral load AUC with the average AUC on at least 1 of the active treatments being lower than the average AUC on placebo.

1.4. Sample Size Justification

The primary endpoint in this study is the AUC of the RSV RNA $\log_{10}$ viral load over 7 days (or up to 11 days if the dose duration is extended up to 10 days).

The primary hypothesis is a positive dose-response relationship for the AUC of active treatment regimens. 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 and a contrast with a positive linear dose-response relationship with respect to active regimens. With respect to multiple contrast testing, multiplicity will be controlled at the pre-specified (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).[1] 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 an O'Brien-Fleming alpha spending function with 3 sequential tests (2 interim, 1 final).[5] As based on 10,000 simulations a sample size of 90 subjects randomized in a 1:1:1 ratio (placebo: low-dose ALS-008176: high-dose ALS-008176) will offer approximately 90% power to detect a positive dose-response relationship as defined assuming an effect size of 0.77 using Cohen's d (ie, the effect size expressed as the ratio of the standard deviation of the AUC) and approximately 80% power assuming an effect size of 0.67 (Cohen's d). Based on the results of the ALS-008176 RSV human challenge study, these effect sizes were considered plausible.[6]

1.5. Randomization and Blinding

Randomization and stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by region (Japan versus non-Japan) and age (≥50 to <65 years and ≥65 years).

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the Interactive Web Response System (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 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. The blind will also be broken for the interim analyses 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 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 Section 10.2 of the protocol; unblinding of study treatment should not necessarily lead to study drug discontinuation.

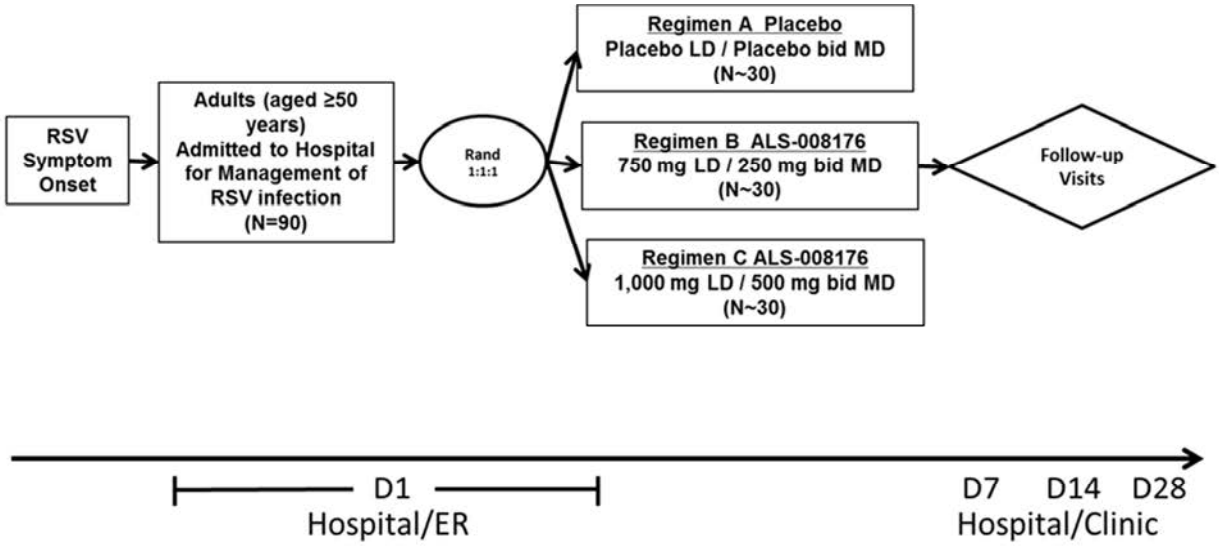
In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed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

2. GENERAL ANALYSIS DEFINITIONS

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

2.1. Visit Windows, Phase Definitions and Baseline

Figure 1: Schematic Overview of the Study



Phases will be constructed as follows:

Trial phase	Start date	End date
Screening (phase 0)	00:00 of the date of signing the informed consent form	1 minute before the first study medication intake
Treatment (phase 1)	Datetime of first study medication intake	Datetime of last study medication intake + 72 hours
Follow-up (phase 2)	End of the phase 1 +1 minute	23:59 of trial termination date (date of last contact).

The last phase, whichever it is for a subject, always ends on 23:59 of the day of trial termination (last contact).

Events will be assigned to phases based on their datetime, but seconds will be ignored overall. If the daypart of the start date of the event is present but the timepart is missing, the event will be treated as if it started at 00:00 on the day of the event. If the daypart of the end date of the event is present but the timepart is missing, the event will be treated as if it happened at 23:59 on the day of the event.

The number of days in the study (reldy) will be 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, where the reference day equals the start date of the treatment phase.

All scheduled assessments after first administration of trial medication will be used. Unscheduled assessments post-dose will not be used in descriptive statistics or any per-time point analysis, but will be used in the determination of the worst-case per treatment, and in listings as applicable.

For assessments on day 1 to 6 and for daily assessments after day 6, the numeric analysis visits (AVISITN) will be equal to the relday.

For assessments on Day 7, Day 10, Day 14 and Day 28, the following table will be used to allocate analysis time points:

Target Day	Analysis time point (numeric version)	Analysis time point	Time interval (days)
7	7	Day 7	[7,9]
10	10	Day 10	[10,12*]
14	14	Day 14	[12*,16]
28	28	Day 28	[17,+∞[
For Katz ADL, DLCO and Spirometry, vital signs and physical examination in outpatients, 12-lead ECG, Mid-tubinate nasal swabs, blood sampling for hematology and biochemistry * Depending on the VISIT label, subjects returning on Day 12 should be assigned to Day 10 or Day 14			
For the analyses per time point in order to have only one evaluation per subject per analysis time point, the following rules will be applied: In case multiple nasal swabs were taken on a single day, the average on the log scale will be used as the value for that subject. For other assessments, if there are two measurements on the same date and/or time, then the measurement with the highest sequence number will be used. If two assessments on different days fall within the same interval, the measurement closest to the target day will be used. If they are equidistant, the last measurement within the interval will be used.			

The baseline record (day 1) is defined as the last record before the first intake of the study drug. For RSV RNA viral load, 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.

On-treatment is defined as the period from the first medication intake until last medication intake + 72 hours (i.e. Treatment Phase).

2.2. Pooling Algorithm for Analysis Centers

If positive treatment effects are found in a trial with appreciable numbers of subjects per centre, 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

The analysis populations covered by this SAP will be:

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.

Safety Set or All Subjects Treated set (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.

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 the central laboratory.

For the interim analysis: a subject is considered to have a confirmed infection with RSV if he/she has been diagnosed with RSV infection based on a PCR-based assay at the local laboratory and for which the RSV infection is confirmed by central laboratory or for which the result of the central laboratory testing is not available at cut-off.

Analyses on the ITT-i Set will be analyzed 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, 8, 9, 10 or 13.

Analyses on the Per-Protocol set will be analyzed as randomized. Note that in the Per-Protocol set subjects will have been treated as randomized by definition.

The Randomized or Treated Analysis set (RT) will be used in all listings. The Safety set or All Subjects Treated set (AST) will be used to perform the evaluation of all safety variables. The Intention-To-Treat-infected set (ITT-i) will be used to perform the evaluation of all efficacy variables. The Per-Protocol (PP) and Intention-To-Treat (ITT) sets will be used to provide supportive analysis of the primary and selected secondary endpoints only (hospital length of stay, hospital discharge readiness, need for and duration of supplemental oxygen and time to clinical stability, ordinal scale score).

2.4. Statistical Methods

This SAP covers the statistical analysis for the final analysis. The interim analysis and IDMC analysis will be described in separate SAPs. Details of the single displays are described in the Data Presentation Specifications (DPS).

- The analysis population will be indicated in the titles of the displays.
- Unless stated otherwise, all results will be presented per treatment group. Tables on subject disposition, exposure, demographic data and baseline disease characteristics will include a 'Total' group, pooling all subjects. Tables on safety will include a "ALS-008176" group.
- Listings will be presented by treatment group and ordered by subject number and time point (if applicable).
- All outputs should be self-explanatory and therefore appropriate footnotes will be provided to clarify the contents of each listing, table or graph.
- In case the X-axis of a graph shows a time component, the distances between the time points will be proportional (not equidistant). Furthermore, when statistics are joined over time by a line, the actual statistics will be depicted by means of a symbol.
- Unless specified otherwise, continuous parameters will be summarized using the following statistics: number of observations, mean, standard deviation, minimum, median and maximum. The mean and median will be presented with one decimal place, while the standard deviation with two decimal places more than the decimal places of the raw data. The minimum and maximum will be presented to the same number of decimal places as the raw data.
- RSV RNA viral load mentioned in this document refers to the RSV RNA viral load qRT-PCR from nasal swab, unless otherwise stated.

2.5. Definition of Subgroups

The following subgroups will be investigated for efficacy (primary and selected secondary endpoints):

Region [Japan, non-Japan]

Age category [≥50 to <65 years and ≥65 years]

Sex [Female, Male]

Baseline RSV Viral load [≤C $\log_{10}$ copies/mL, >C $\log_{10}$ copies/mL] with C = rounded median

Comorbidities [Yes, No]

Use of systemic corticosteroids prior to treatment with ALS-008176 [Yes, No]

Duration of RSV symptoms prior to first treatment [≤3 Days; >3 Days]

Baseline viral subtype [RSV A; RSV B]

Completion of planned study therapy

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

Region [Japan, non-Japan]

Age category [≥50 to <65 years and ≥65 years]

Race [Caucasian, Black, Asian, Other]

BMI [<25; 25-<30; ≥30]

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 associated with risk for lower respiratory tract disease[1][2]
  - Asthma [Yes/No]
  - COPD [Yes/No]
  - CHF [Yes/No]
  - CAD (coronary artery disease) [Yes/No]
- Other conditions/therapy of potential interest due to risk of infections in general:
  - Diabetes mellitus [Yes/No]
  - CRF (Chronic Renal Failure) [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.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

The IDMC will review the safety data initially after approximately 12 subjects have completed treatment and when approximately 12 Japanese subjects have completed treatment to assess that treatment may safely continue in each arm. A separate SAP will be written that provides details on the data package for this purpose. Details on operational characteristics will be provided in the IDMC Charter.

In addition, a maximum of 2 interim analyses are planned to assess the primary endpoint for early superiority and futility. The first interim analysis will be performed when at least 45 subjects have been randomized, preferably after the end of a hemispheric RSV season. Up to the final database lock, the study team will remain blinded to the results. Details on operational characteristics will be provided in the interim analysis charter. An Interim Analysis SAP will be written that describes this formal interim analysis, focusing on the rules of futility, early superiority and sample size recalculation.

This interim analysis will be based on the subjects randomized up to that timepoint in the ITT-i Set.

The following situations will be considered based on the results of the primary analysis at this stage: that the study is considered futile; that superiority can be concluded (based on an O'Brien-Fleming alpha spending function); that the study is considered underpowered; or that the study should continue unchanged. In the case of the (unbinding) futility boundary or the superiority boundary being crossed, the IDMC will recommend early termination to the Sponsor Committee. If the study is considered underpowered, a sample size increase may be suggested to a maximum of 180 subjects. This blinded sample size calculation will take the residual error variance into account of the primary analysis model.

If early superiority on the primary endpoint can be established, the study may, however, 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. However, at the interim analyses or at any time, upon recommendation by the IDMC, a dose regimen may be removed or adjusted based on PK, safety, and/or antiviral activity considerations.

The 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.

4. ANALYSES

4.1. SUBJECT INFORMATION

All general analyses will be done on the ITT-i Set and the Safety Set, unless specified otherwise for a specific display.

4.1.1. Demographics and Baseline Characteristics

All demographics and baseline characteristics will be summarized overall and by treatment group. Descriptive statistics or frequency tabulation will be provided for the following parameters.

Demographic parameters:

Sex (Male, Female, Undifferentiated)

Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other). The specification of the category 'Other' will only be listed.

Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Country (from [DM] dataset)

Geographic region (based on country: North America [to include Puerto Rico], Europe, South America, Asia-Pacific)

Age (years)

Weight at baseline (kg)

Height at baseline (cm)

BMI at baseline = 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)

Baseline disease characteristics:

Duration of RSV symptoms prior to first treatment (days)

Presence of comorbidities (yes, no)

Comorbid diseases associated with risk for lower respiratory tract disease[1][2] (yes, no) and proportion of subjects suffering from each of the following diseases:

- Asthma
- COPD
- CHF
- CAD (coronary artery disease)

Other conditions/therapy of potential interest due to risk of infections in general (yes, no) and proportion of subjects with each of the following conditions/therapies:

- Diabetes mellitus
- CRF (Chronic Renal Failure)
- Use of systemic corticosteroids (PO, IV) prior to or during the treatment

Baseline RSV Viral load ($\log_{10}$ copies/mL)

Previous use of aerosolized ribavirin (yes, no)

Previous use of IV immunoglobulin (yes, no)

Oxygen Saturation (%)

Receiving Supplemental Oxygen (yes, no)

Intravenous or enteral tube feeding (yes, no)

Intravenous or enteral tube hydration (yes, no)

Respiratory Rate (breaths/min)

Heart Rate (beats/min)

4.1.2. Disposition Information

Summaries will be provided for the following disposition information:

- Number of subjects screened, screen failures, randomized or treated, not randomized, randomized and not treated, treated and not randomized, safety set, randomized and treated, treated but not RSV infected, treated and RSV infected and per protocol set.
- Number of subjects who completed or discontinued treatment and the trial, with a breakdown of the reasons of discontinuation.
- Number of subjects per phase and per visit in the trial.

4.1.3. Treatment Compliance

Dosing compliance is calculated as the actual number of doses taken, as a percentage of the planned number of doses. The actual number of doses can be calculated from the number of doses dispensed (18 tablets) minus the number of doses returned (from [da] data set: number of tablets returned). The planned number of tablets is 12. In case the length of duration is increased, the calculation will take the new planned number into account.

Dosing compliance will be summarized descriptively by treatment group.

4.1.4. Extent of Exposure

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.

Actual treatment duration will be summarized descriptively by treatment group.

4.1.5. 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.

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.

4.1.6. Medical History

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

4.1.7. Preplanned Surgeries/Procedures

Preplanned surgeries and procedures will be listed.

4.1.8. Prior and Concomitant Medications

Medications taken 14 days before the Screening Visit and up to the Safety Follow-up Visit will be summarized by preferred term using the World Health Organization-Drug Dictionary for the ITT-i Set 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.

4.2. EFFICACY

The efficacy analyses include the following primary, secondary and exploratory endpoints.

Primary endpoint

- RSV RNA $\log_{10}$ viral load (measured by qRT-PCR in the mid-turbinate nasal swab specimens) AUC from immediately prior to first dose of study drug (baseline) until Day 7 (or up to 11 days if the dose duration is extended to up to 10 days).

Secondary endpoints

- RSV clinical course endpoints:

- Length of hospital stay from admission to discharge and from study treatment initiation to discharge.

- Length of hospital stay from admission to readiness for discharge and from study treatment initiation to readiness for discharge, with readiness for discharge defined by the investigator.

- Need for and duration of intensive care unit (ICU) stay.

- Need for and duration of supplemental oxygen (regardless of method used).

- Number of hours until peripheral capillary oxygen saturation (SpO2) ≥93% on room air among subjects who were not on supplemental oxygen prior to current hospitalization.

- Respiratory rate, SpO2, and body temperature return to pre-RSV disease level.

- Need for and duration of noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy).

- Time to return to pre-RSV functional status (Katz ADL score).

- Need for hydration and feeding by IV catheter/enteral tube.

- Time to clinical stability defined as the time at which the following criteria are all met:

    - normalization of blood oxygen level (return to baseline; by pulse oximetry) without requirement of supplemental oxygen beyond baseline level

    - normalization of oral feeding

    - normalization of respiratory rate

    - normalization of heart rate

- Improvement on the ordinal scale
- All-cause mortality.

- RSV RNA viral load as measured by qRT-PCR of the mid-turbinate nasal swab specimens which will be used to determine the following:

- Viral load over time.
- Peak viral load, time to peak viral load, rate of decline of viral load, and time to RSV RNA viral load being undetectable.
- Proportion of subjects with undetectable viral load at each time point.
- RSV RNA viral load AUC from immediately prior to first dose of study drug (baseline) until Day 10 and until Day 14.

Exploratory endpoints

- The amount of:

- Supplemental oxygen above pre-RSV disease level (regardless of method used) from study treatment initiation to Day 7.
- Oxygen delivered by noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy).
- Subjects (proportion) who started antibiotic use after the first dose of the study drug.

- Disease status and presence of complications with onset after treatment initiation:

- Bacterial superinfections reported as AEs (eg, pneumonia, acute otitis media, sinusitis, bronchitis, bacteremia).
- Exacerbations of underlying pulmonary disease (eg, asthma, chronic obstructive pulmonary disease).
- Cardiovascular and cerebrovascular events (eg, myocardial infarction, congestive heart failure exacerbation, arrhythmia, stroke).
- Respiratory failure
- *Clostridium difficile* associated diarrhea
- Other

- Duration and severity of signs and symptoms of RSV infection as assessed by the respiratory infection patient-reported outcome (RI-PRO) questionnaire and additional questions about health and functioning completed by the subject in the eCOA.
- HRQoL assessed by the EuroQoL 5 Dimension visual analogue scale (EQ-5D VAS) completed by the subject in the eCOA.
- Hospital readmission for respiratory reasons up to the Day 28 follow-up visit.
- RSV RNA viral load (AUC) as measured by qRT-PCR of endotracheal samples in intubated subjects.
- Lung function measured by the DLCO and spirometry test.
- RSV infectious viral load as measured using a quantitative viral culture (plaque assay).

4.2.1. Analysis Specifications

All efficacy analyses will be analyzed in the ITT-i set (except for the primary endpoints and selected secondary endpoint which will also be analyzed on the ITT and PP Sets) and will be tabulated per treatment group for each stratum separately (region and age) and per treatment group overall (over all strata).

4.2.1.1. Level of Significance

The primary hypothesis is a positive dose-response relationship for the AUC of active treatment regimens. 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 and a contrast with a positive linear dose-response relationship with respect to active regimens. With respect to multiple contrast testing, multiplicity 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)[1]. 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 an O'Brien-Fleming alpha spending function with 3 sequential tests (2 interim, 1 final)[5].

4.2.2. Data Handling Rules

For analysis purposes the log10 qRT-PCR viral load will be imputed with 0 when the result is 'negative', and the midpoint on the log scale between the limit of detection and limit of quantification when the result is 'positive' but non-quantifiable.

4.2.3. Primary Efficacy Endpoint

4.2.3.1. Definition

The primary estimates of the AUC will be derived from a mixed model (see section 4.2.3.2 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 (Day 1) 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.
- If for the baseline assessment the central laboratory value is missing, the value that will be imputed is based on the average value as based on the analysis population (ITT-i, ITT or PP population).
- For all post-baseline days the RSV RNA viral load result of the swab that was performed at that day will be used, counting from the Day of first treatment which is defined as Day 1.
- In case multiple nasal swabs were taken on a single day the average 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 calculated by the trapezoidal summation rule, based on planned days of sampling (Baseline visit up till/including Day 7 visit, or up to 11 days if the dose duration is extended to up to 10 days), including the timepoints with (imputed) values available:

$$AUC_{0-7\ days} = \frac{1}{2}\sum_{i=1}^{n}(y_i + y_{i-1}) \times (t_i - t_{i-1})$$

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 baseline log 10 viral load. t_0 is time 0.

The following additional rules, on top of the rules of the primary analysis, will be applied to deal with missing values post-baseline before calculating the Viral load AUC:

- Missing value between baseline and day 7 will be imputed by intrapolation.
- If the last observations are missing, the last available observation will be carried forward. Unscheduled assessments will be included and will be eligible for carrying forward.

4.2.3.2. 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, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-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 log10 viral load measured at Day 1.

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 O'Brien-Fleming (OBF) α spending function.

$\alpha^*(t') = 2 - 2\phi\ (Z_{\alpha/2}\ /\sqrt{t'})$

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 (=90) and ϕ denotes the standard normal cumulative distribution function.

The *lower* option is selected as the contrast needs to have a value below zero (ie, there needs to be a reduction in AUC 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 OBF critical value.

The differences in the AUCs 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 as calculated using the trapezoidal rule will be considered as a supportive analysis and will be analyzed using a linear model with AUC as a dependent variable and treatment group and stratum as fixed factors, and baseline log10 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.

4.2.4. Secondary Efficacy Endpoints

4.2.4.1. Definition

Formulae to be used for derived variables, including data conversions, are provided in Table 1. In the derivation of durations described below, no imputation of the start and/or end date/time will be performed.

Table 1. Calculations and Conversion Formulae

Measurement	Formula
Length of hospital stay (hours) [Time-to event] Time to readiness for discharge (hours) [Time-to-event]	(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal 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 prior to an event the time of death will be taken as censoring time (or 12:00 if not available).
Length of hospital stay since hospital admission (hours) [Time-to event] Time to readiness for discharge since hospital admission (hours) [Time-to-event]	(Date and time of event or censoring - date and time of hospital admission)/3600, rounded to one decimal 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 prior to an event the time of death will be taken as censoring time (or 12:00 if not available).
ICU duration of stay (hours) [Duration] Duration of supplemental oxygen (hours) [Duration] (3 separate parameters: supplemental oxygen, invasive ventilator, non-invasive ventilator) Need for feeding, hydration by IV catheter/enteral tube (hours) [Duration] (2 separate parameters)	sum of [(end date and time of event - start date and time of event)/3600], rounded to one decimal If the end date is missing, the end date is considered to be after study completion or withdrawal. 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 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.
Time to end of Oxygen supplementation (hours)	(Date and time of event or censoring - date and time of first dose of

[Time-to-event] (3 separate parameters: overall, invasive, non-invasive) Time to end of supplementation feeding, hydration (hours) [Time-to-event] (2 separate parameters)	study drug)/3600, rounded to one decimal The event is defined as the last end date and time of the measured parameter (supplemental oxygen, invasive oxygen, non-invasive oxygen, feeding or hydration). If this 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 last end date and time of the measured parameter 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 prior to the last end date and time of the measured parameter, the time of death will be taken as censoring time (or 12:00 if not available). If no oxygen supplementation, supplemental feeding or hydration was necessary post baseline, the value will be set to 0.
Time point of SpO2 ≥ 93% on room air	The first time point with SpO2 ≥ 93%, where no supplemental oxygen supplementation is given at or after this time point and where no value < 93% are measured after this time point.
Time to SpO2 ≥ 93% (hours) on room air [Time-to-event]	minimum[date and time of time point with SpO2 ≥ 93% on room air, date and time of last SpO2 measurement] - date and time of first dose of study drug)/3600†, rounded to one decimal Subjects with SpO2<93% on room air or who are still on oxygen supplementation at the last SpO2 assessment will be censored at the date and time of the last SpO2 assessment. This parameter will only be calculated for subjects who were not on supplemental oxygen prior to current hospitalization
Time point of return to pre-RSV disease level (hours) for HR, RR, SpO2 (3 separate parameters)	The first time point where it is indicated by the investigator that the observed value is normal for the subject, and for none of the time points after this point in time the values are indicated to be abnormal for the subject (separate for HR, RR or SpO2).
Time to return to pre-RSV disease level (hours) for HR, RR, SpO2 [Time-to-event]	(minimum[date and time of time point of return to pre-RSV disease level, date and time of last measurement] - date and time of first dose of study drug)/3600, rounded to one decimal If none of the values are indicated to be abnormal for the subject, this value will be set at time 0. Subjects with an abnormal value at the last assessment will be censored. Subjects for which this last assessment is the baseline

	assessment will be censored at time 0.
Time to return to pre-RSV disease feeding status (hours) [Time-to-event]	(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal All subjects are assumed to have no supplemental feeding pre-RSV. The event is defined as the last available end date and time supplemental feeding was provided. If this 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 prior to an event the time of death will be taken as censoring time (or 12:00 if not available). If no supplemental feeding was necessary post baseline, the value will be set to 0.
Time to Clinical Stability [Time-to-event]	maximum[time to return to pre-RSV disease level for SpO2, RR and HR, feeding] Subject will be censored if the subject is censored for at least 1 of the 4 time to parameters at the minimum of the available data. If no data are available the time will be censored at 0 hours.
Time point of return to normal temperature (hours) [Time-to-event]	All subjects are assumed to have a normal temperature level pre-RSV disease Time point of return to pre-RSV disease level temperature is defined as the first time point with a normal temperature and no time points after that time point with an abnormal value. The normal limits to be used are: - Axillary: 36.1 – 38.0 - Forhead: 36.1 – 38.0

	– Oral: 36.1 – 38.0 – Rectal: ≤ 37.2 – Tympanic: ≤ 37.8 If there were no abnormal values post baseline, the value will be set at 0 hours.
Time to normal temperature (hours) [Time-to event]	Minimum[date and time of Time of return to pre-RSV disease level temperature, date and time of last measurement] - date and time of first dose of study drug)/3600†, rounded to one decimal If none of the values are abnormal for the subject, this value will be set at time 0. Subjects with an abnormal value at the last assessment will be censored. Subjects for which this last assessment is the baseline assessment will be censored at time 0.
Time point of return to pre-RSV functional status (KATZ ADL score)	The first time point where the KATZ ADL score is equal or higher than the pre-RSV disease KATZ ADL score and no lower scores are measured after this time point. Functional status is the total points on the KATZ Index of Independence in Activities of Daily Living (KATZ ADL score)
Time to return to pre-RSV functional status (KATZ ADL score) (days) [Time-to-event]	minimum[date and time of time of return to pre-RSV functional status, date and time of last measurement] - date and time of first dose of study drug)/3600, rounded to one decimal If the KATZ ADL score is never lower than the pre-RSV score, this value will be set at time 0. Subjects with a functional status lower than the pre-RSV disease functional status at the last KATZ ADL assessment will be censored. Subjects for which this last assessment is the baseline assessment will be censored at time 0.
Ordinal scale score	The value as collected in the eCRF on the day of last dose (Day 5/6 depending on timing of LD) will be used as score on the day of last dose. Only in case of a missing score, the score will be calculated based on the available information in the eCRF. The 6 categories to be considered are:

	• Death • Admitted to ICU • Non-ICU hospitalization requiring supplemental oxygen • Non-ICU hospitalization not requiring supplemental oxygen • Not hospitalized, unable to resume normal activities • Not hospitalized, resumption of normal activities Subjects will receive a score ranging from 1 (=subject died on or before of their day of last dosing) to 6 (=subject was not-hospitalized, resumptions of normal activity) depending on his status on day of last dosing For days 3 to 14, the ordinal scale will be calculated on each day, using the algorithm described above.
All-cause mortality	Subjects who died during the study will receive code 1, subjects who survive will receive code 0
Peak viral load	Highest value of viral load at or after the baseline measurement.
Time to peak viral load (hours) [Time-to-event]	Defined as the relative time in hours from the first dose of study drug until the first time point when the viral load reaches the peak viral load. 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. Subjects for which this last assessment is the baseline assessment will be censored at time 0.
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.
Time to non-detectability (hours) [Time-to-event]	Defined as the relative time in hours from the first dose of study drug until the first post baseline time point when the viral load reaches non-detectability and no detectable values are measured after this time point. For each subject in the ITT-i it will be assumed that the subject is positive at baseline (even if the value is negative). Subjects whose viral load does not reach non-detectability will be censored at the relative time in hours from the first dose of study drug until this last RSV assessment. Subjects for which this last assessment is the baseline assessment will be censored at time 0.
Time to non-detectability (hours) [interval censored]	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.
Log viral load area under the curve from baseline to 10 days post first dose of study drug ($AUC_{0\text{-}10\ days}$).	The $AUC_{0–10\ days}$ will be derived based on trapezoid method: $AUC_{0-10\ days} = AUC_{0-7\ days} + \frac{3}{2}(y_7 + y_{10})$ where y_7 is the log 7 viral load at day 10 and $y_{10}$is the log 10 viral load at day 10. The following rules will be applied to deal with missing values before calculating the Viral load AUC: • If the last observations are missing, the last available observation will be carried forward. Unscheduled assessments will be included and will be eligible for

	carrying forward until Day 10. • In case multiple nasal swabs were taken on a single day the average on the log scale will be used as the value for that subject.
Log viral load area under the curve from baseline to 14 days post first dose of study drug ($AUC_{0\text{-}14\ days}$).	The $AUC_{0–14\ days}$ will be derived based on trapezoid method: $AUC_{0-14\ days} = AUC_{0-10\ days} + \frac{4}{2}(y_{10} + y_{14})$ where y_{10} is the log 10 viral load at day 10 and $y_{14}$is the log 10 viral load at day 14. The following rules will be applied to deal with missing values before calculating the Viral load AUC: • If the last observations are missing, the last available observation will be carried forward until Day 14. • In case multiple nasal swabs were taken on a single day the average on the log scale will be used as the value for that subject.

4.2.4.2. Analysis Methods

To compare incidences across treatment groups (for the need for ICU stay, oxygen support, supplemental feeding or supplemental hydration, for the all-cause mortality, for the subjects with undetectable viral load per time point and for the presence of complications), logistic regressions will be used, with treatment as fixed effects and strata as part of the stratifying variables (ie. stratified logistic model). Other covariates and or baseline indicators may be included in the model when of predictive value, such as baseline log_{10} viral load, smoker (yes/no), the presence/absence of co-morbid diseases, presence/absence of co-morbid 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 costicosteroids, supplemental oxygen at baseline and age as continuous variable. Stepwise selection will be used to identify the prognostic factors for each of the different models for the different incidence parameters. 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. 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).

Time-to-events variables will be analyzed in an exploratory sense using Kaplan-Meier analysis, A summary table including number of subjects included in the analysis, number of subjects censored, 25th and 75th percentiles and median time to even, 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.

If specified, time-to-events variables will also 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 strata, as well as the continuous covariates of baseline $\log_{10}$ viral load. Other covariates may be included when of predictive value, such as smoker (yes/no), presence/absence of co-morbid diseases, presence/absence of co-morbid 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 costicosteroids, supplemental oxygen at baseline and age as continuous variable. As in the logistic regression, a significance level of 0.05 will be used for a variable to enter the model and a significance value of 0.10 to stay in the model. A summary of information from the final model will include parameter estimates and associated standard errors, estimated accelerated failure time ratios versus placebo and associated 95% confidence intervals, and p-values.

Length of Hospital Stay/Length of Hospital Need

The Length of Hospital Stay/Need (both since treatment initiation and since hospital admission) will be summarized and listed. The Length of Hospital Stay/Need will be analyzed in an exploratory manner using Kaplan-Meier analysis.

Length of Hospital Stay/Need will also be compared between each active treatment group and placebo using an accelerated failure time (AFT) model as described above.

Need and Duration of ICU Stay

The need for ICU stay will be analyzed on the subgroup of subjects who were not in the ICU before the first dose of study medication. The duration in the ICU will be analyzed all subjects and on both the subgroup who were and who were not in the ICU before the first dose of study medication.

The number and percentage of subject with need of ICU stay, and the duration of ICU stay in hours, will be summarized descriptively.

To compare incidence of the need for ICU stay across treatment groups, (exact) logistic regression as described before will be used.

Need and Duration of Oxygen Support, Supplemental Feeding, Supplemental Hydration

The need and duration of supplemental oxygen will be analyzed by splitting the ITT-i population into two partitions:

1) Those patients who require supplemental oxygen before treatment initialization

2) Those patients who did not require supplemental oxygen before treatment initialization

Both partitions will be analyzed separately, answering two different questions:

1) For those patients who require supplemental oxygen before treatment initiation: Is there a treatment difference in the time to no longer requiring supplemental oxygen? This analysis will be performed primarily with a Kaplan-Meier analysis and a stratified Gehan test.

2) For those patients who did not require supplemental oxygen before treatment initialization: Is there a treatment difference in preventing the use of supplemental oxygen? This partition will be analyzed using a stratified (exact) logistic regression model as specified above.

While we cannot integrate these results 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].

In addition to the analysis described above, the time to no longer requiring supplemental O2 will be analyzed on the total group of subjects where subjects who do not require supplemental oxygen during the study are considered to have their event at time 0. As before, this will be analyzed in an exploratory sense using Kaplan-Meier analysis and with a stratified Gehan test to test for treatment differences.

This analysis will be repeated by method of administration (invasive, non-invasive).

The analysis for the need and duration of supplemental feeding and supplemental hydration will be done in similar fashion as for supplemental oxygen use described above.

Time to SpO2 ≥ 93% (hours) on room air

Time to SpO2 ≥ 93% (hours) on room air will be summarized and listed for subjects who were not on supplemental oxygen prior to current hospitalization.

Among subjects who were not on supplemental oxygen prior to current hospitalization, the time to SpO2 ≥ 93% (hours) on room air, will be summarized and analyzed in an exploratory sense using Kaplan-Meier analysis.

The time from first dose to SpO2 ≥ 93% (hours) on room air will also be analyzed using AFT methodology.

Time to return to pre-RSV disease level (hours) for RR, SpO2; body temperature

The time to return to pre-RSV disease level (hours) for RR, SpO2 and body temperature will be analyzed using the same approach as for the Time to SpO2 ≥ 93% (hours) on room air.

Time to return to pre-RSV functional status (KATZ ADL score) (days)

Time to return to pre-RSV functional status (KATZ ADL score) (days) will be analyzed using the same approach as for the Time to SpO2 ≥ 93% (hours) on room air.

Time to clinical stability (hours)

The time to clinical stability (hours) will be analyzed using the same approach as for the Time to SpO2 ≥ 93% (hours) on room air.

Ordinal scale

The number and percentage of subjects will be summarized for the ordinal scale by treatment group at the end of the treatment period (Day 5/6).

The analysis will be performed using a proportional odds model, modeling the common odds ratio of the improvement on the ordinal scale of each active treatment versus control. Age category (≥50 to <65 years and ≥65 years) and region (Japan, non-Japan) will be added to the model as fixed factors. For each of the 5 possible cut-points the odds ratio will also be presented (comparing active versus placebo) to verify the common odds assumption.

For the ordinal scale also descriptive statistics will be computed for each post-baseline day (days 3 to 14 and day of last dose). Here missing data will be imputed using the LOCF approach.

All-cause mortality

The number and percentage of subjects who died will be summarized and compared between treatment groups using the logistic regression approach described before.

Note that this analysis will only be performed if any deaths did occur.

Viral load over time

Descriptive statistics and mean (SE) plots will be shown for the log10 values of RSV RNA viral load and the changes from baseline calculated in log10(copies/ml) by treatment group.

Peak viral load/Rate of decline:

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. Other covariates and or baseline indicators may be included in the model when of predictive value, such as baseline $\log_{10}$ viral load, smoker (yes/no), presence/absence of co-morbid diseases, presence/absence of co-morbid 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 costicosteroids, supplemental oxygen at baseline and age as continuous variable. Stepwise selection will be used to identify the prognostic factors. 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.

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.

Time to Peak viral load:

Time to Peak viral load will be analyzed using the same approach as for the Time to SpO2 ≥ 93% (hours) on room air.

Time to RSV RNA being undetectable:

Time to RSV RNA being undetectable will be analyzed using the same approach as for the Time to SpO2 ≥ 93% (hours) on room air.

In addition, the differences in time to RSV RNA being undetectable of active dosing regimens versus placebo treatment will 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 titer 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 titer value and weighted average for each stratum.

Proportion of subjects with undetectable viral load at each time point:

The proportion of subjects with a negative viral shedding titer will be tabulated at each timepoint (with corresponding 95% CI). In addition, the same logistic regression approach as described before will be used to obtain the odds ratios (95% CI) for each comparison versus placebo.

RSV RNA viral load AUC until Day 10 and until Day 14

The same model used for the primary analysis will be used to test for a dose response relationship on the AUC until Day 10 and until Day 14. No corrections for multiplicity will be made, thus the significance level of *alpha* (α^*) will be kept at 0.05.

The differences in the AUCs for active versus placebo will be derived using appropriate contrasts deriving least square mean differences, including the 95% 2-sided confidence intervals.

4.2.5. Patient Reported Outcomes

4.2.5.1. Respiratory Infection Symptom Questionnaire (RSV-PRO)

4.2.5.1.1. Definition

The RSV Patient-Reported Outcome (RSV-PRO) measure is a 32-item patient-reported questionnaire used to assess the severity of RSV symptoms over the past 24 hours and is exactly the same questionnaire as the FLU-PRO questionnaire.

The presence and severity of RSV signs and symptoms are assessed across 6 body systems affected by RSV: Nose (4 items), Throat (3 items), Eyes (3 items), Chest/Respiratory (7 items), Gastrointestinal (4 items), and Body/Systemic (11 items) with 5 possible levels (not at all (level code = 0), a little bit (level code = 1), somewhat (level code=2), quite a bit (level code=3), very much (level code = 4).

The RSV-PRO domain scores are defined as indicated in **Table 2**. These will be calculated at each time point a questionnaire was filled. A change from baseline will also be calculated.

Table 2. RSV-PRO domain scores

Domain	Items	Scoring	Minimum Data Requirement
Nose	Runny or dripping nose Congested or stuffy nose Sneezing Sinus pressure	Arithmetic mean of 4 items within Nose domain	Daily score for 3 of 4 items must be present to calculate domain score
Throat	Scratchy or itchy throat Sore or painful throat Difficulty swallowing	Arithmetic mean of 3 items within Throat domain	Daily score for 2 of 3 items must be present to calculate domain score
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	Arithmetic mean of 3 items within Eyes domain	Daily score for 2 of 3 items must be present to calculate domain score
Chest/Respiratory	Trouble breathing Chest congestion Chest tightness Dry or hacking cough Wet or loose cough Coughing Coughed up mucus or phlegm	Arithmetic mean of 7 items within Chest/Respiratory domain	Daily score for 5 of 7 items must be present to calculate domain score
Gastrointestinal	Felt nauseous Stomach ache How many times did you vomit? How many times did you have diarrhea?	Arithmetic mean of 4 items within Gastrointestinal domain	Daily score for 3 of 4 items must be present to calculate domain score
Body/Systemic	Headache	Arithmetic mean of	Daily score for 8 of 11

	Head congestion Felt dizzy Lack of appetite Sleeping more than usual Body aches or pains Weak or tired Chills or shivering Felt cold Felt hot Sweating	11 items within Body/Systemic domain	items must be present to calculate domain score
Total	All above 32 items	Arithmetic mean of all 32 items within RSV-PRO	In the presence of missing data, the above conditions for the calculation of all domain scores must be met in order to calculate the RSV-PRO total score.

Table 3. Calculations and Conversion Formulae

Measurement	Formula
Time to alleviation from RSV-like symptoms	Alleviation or "recovery" from RSV-like symptoms in adults with acute, laboratory confirmed RSV is defined as the first day a subject reports a RSV-PRO total score ≤1.0 AND all domain scores are ≤1.0. Subjects with an abnormal value at the last assessment will be censored at the date and time of the last assessment
Time to alleviation from systemic and respiratory symptoms	Alleviation or "recovery" from systemic and respiratory symptoms is defined as the first day a subject reports 'not at all' or 'a little bit" as severity for all items in the body/systemic and respiratory domain. Subjects with an at least moderate score at the last assessment for these 2 domains will be censored at the date and time of the last assessment

4.2.5.1.2. Analysis Methods

Actual values and changes from baseline will be summarized by treatment group at each scheduled time point for the RSV-PRO domain and total scores. Mean±SE graphs over time for the actual values and changes from reference will be presented.

Time-to-alleviation will be analyzed in an exploratory sense using 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. For each comparison of active versus placebo the stratified Gehan test will also be presented.

Frequency tabulation of each of the 32 items at the time point of return to return to usual activities and time point of return to usual health as defined in section 4.2.5.2.1.

4.2.5.2. Adult RSV Additional Questions

4.2.5.2.1. Definition

Table 4. Calculations and Conversion Formulae

Measurement	Formula
Time to return to usual activity	The time in hours from the first dose of investigational product till the first one of 2 successive cases where the response is 'Yes' on RSV-PRO additional question 7 ("have you returned to your usual activities?") . Time points with missing data are ignored in this analysis. The successive recordings cannot be within the same window. In case there are 2 recordings within a single window (i.e. morning window, afternoon window or evening window) the worst case within that window will be taken. In cases where there are no sufficient recordings, the endpoint will be censored. Censoring will be at time of the last assessment if ticked as "Yes"; otherwise censoring will be the first window after the last assessment (lower limit). One exception is censoring at the Day 28 Visit (last study day for the subject). If the subject is not returned to usual activities/health on this day, the time of the last diary entry will be taken as the time of censoring.
Time to return to usual health	The time in hours from the first dose of investigational product till the first one of 2 successive cases where the response is 'Yes' on RSV-PRO additional question 9 ('have you returned to your usual health?'). Time points with missing data are ignored in this analysis. The successive recordings cannot be within the same window. In case there are 2 recordings within a single window (i.e. morning window, afternoon window or evening window) the worst case within that window will be taken. In cases where there are no sufficient recordings, the endpoint will be censored. Censoring will be at time of the last assessment if

	both items are ticked as "Yes"; otherwise censoring will be the first window after the last assessment (lower limit). One exception is censoring at the Day 28 Visit (last study day for the subject). If the subject is not returned to usual activities/health on this day, the time of the last diary entry will be taken as the time of censoring.
Time to full recovery	The maximum of the time to return to usual activity and usual health when both have an event, or the minimum of censored time(s) if at least one is censored.

4.2.5.2.2. Analysis Methods

Time to return to usual activity and usual health

Kaplan-Meier curves will be provided by treatment group. For each comparison of an active group versus placebo the stratified Gehan test will also be presented.

Other RSV additional questions

The number and percentage of subjects per category will be tabulated over time by treatment group for items 1 to 6 and item 8 of the RSV additional questions.

4.2.5.3. EQ-5D

4.2.5.3.1. Definitions

The EQ-5D questionnaire will be analyzed in 3 ways:

1) EQ-5D descriptive system: 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 possible levels (no (level code = 1), slight (level code = 2), moderate (level code=3), severe (level code=4), unable to/extreme (level code = 5).

Dimension		**Level**		**Interpretation**
1	Mobility	1	No problems	I have no problems in walking about
		2	Slight problems	I have slight problems walking
		3	Moderate problems	I have moderate problems walking
		4	Severe problems	I have severe problems walking
		5	Unable to	I am unable to walk
2	Self-care	1	No problems	I have no problems washing or dressing myself
		2	Slight problems	I have slight problems washing or dressing myself
		3	Moderate problems	I have moderate problems washing or dressing myself
		4	Severe problems	I have severe problems washing or dressing myself
		5	Unable to	I am unable to wash or dress myself
3	Usual activities	1	No problems	I have no problems doing my usual activities

		2	Slight problems	I have slight problems doing my usual activities
		3	Moderate problems	I have moderate problems doing my usual activities
		4	Severe problems	I have severe problems doing my usual activities
		5	Unable to	I am unable to do my usual activities
4	Pain/discomfort	1	No pain	I have no pain or discomfort
		2	Slight pain	I have slight pain or discomfort
		3	Moderate pain	I have moderate pain or discomfort
		4	Severe pain	I have severe pain or discomfort
		5	Extreme pain	I have extreme pain or discomfort
5	Anxiety/ depression	1	Not anxious	I am not anxious or depressed
		2	Slightly anxious	I am slightly anxious or depressed
		3	Moderate anxious	I am moderately anxious or depressed
		4	Severe anxious	I am severely anxious or depressed
		5	Extreme anxious	I am extremely anxious or depressed

2) EQ-5D VAS: a continuous score ranging from 0 to 100.

3) EQ-5D Valuation index: The information of the 5 dimensions of the descriptive system summarized into one index.

   a. Assign the level code 1, 2, 3, 4 and 5 to each level of the 5 dimensions (see table)

   b. Create a health state for each patient-time point combination. A health state is a combination of 5 level codes; one level code for each dimension. The dimensions are ordered as described in the table above. E.g. health state 12311 indicates 'no problems in walking about, slight problems washing or dressing myself, moderate problems to perform my usual activities, no pain or discomfort, not anxious or depressed'.

   c. Assign an index value to each health state as defined on the EUROQol website (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html). EQ-5D health state is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The algorithm is based on the valuation of EQ-5D health states using the UK TTO (=time trade-off method) based value set. Based on the origin of the subjects, another method can be used.

4.2.5.3.2. Analysis Methods

Actual values and changes from baseline will be summarized by treatment group at each scheduled time point for the EQ-5D VAS and valuation index. Mean±SE graphs over time for the actual values and changes from reference will be generated.

The number and percentage of subjects per problem level will be tabulated over time by treatment group for each of the 5 dimensions.

This will be done for all subjects and in addition for the following subgroup: ≥50 to <65 years and ≥65 years.

4.2.5.4. Katz-ADL

4.2.5.5. Definition

Katz-ADL is a status descriptor. A status change will be considered RSV-related if the subject evolved from independence before the RSV infection to dependence during or after RSV infection for each of the 6 different activities.

Measurement	Formula
Normalized Katz-Score	The normalized Katz score is the ratio of the actual Katz-score over the Katz-score pre-onset of RSV symptoms

4.2.5.5.1. Analysis

For each day the average Katz score will be presented by treatment group, as well as the change from baseline using both raw scores as normalized scores. Data will be presented using a mean (SE) plot over time, by treatment group.

The evolution of activities of Daily Living (ADL) as assessed by the Katz ADL will be analyzed by analyzing the time to return to pre-RSV functional status (Katz ADL score) as described in section 4.2.4.2.

Additionally, a cross-tabulation of the status changes versus the status before the RSV infection will be presented for each of the 6 different activities, over time and at the time of hospital discharge. This table will show the number and percentage of subjects with dependence and the number and percentage of subjects with an RSV-related status change.

<u>The relationship between RSV RNA viral load and Katz ADL</u>

The relationship between the RSV RNA (as measured by the PCR method) will be assessed using spearman rank correlation between the viral load and the Katz ADL normalized score for each combination of Days. This matrix of correlations will provide information if within each day the viral load is predictive of Katz functional status, but will also allow if there is a delayed relationship, meaning that viral load is predictive of future Katz functional statuses. A second approach will be to correlate the time to virus negativity with the Katz ADL baseline score marking censored cases. Other methods may be considered as appropriate.

<u>The relationship between the Katz ADL and the subject eCOA responses.</u>

The relationship between the Katz ADL and the scores of eCOA will be assessed using various measures. Katz baseline scores will be correlated with the time to alleviation from systemic and

respiratory symptoms as defined by the RSV-PRO. Subjects who are censored will be assumed to have alleviation of symptoms 1 day after censoring in this analysis. For the multidimensional aspects of the various patient reported measurements and the Katz scores and viral load a separate analysis plan will be issued.

4.2.6. Other Efficacy Variable(s)

4.2.6.1. Definition

Formulae to be used for derived variables, including data conversions, are provided in **Table 5**. In the derivation of durations described below, no imputation of the start and/or end date/time will be performed.

Table 5. Calculations and Conversion Formulae

Measurement	Formula
Time to onset of complications after initiation of treatment	Defined as the relative time in days from the first dose of study drug until the first occurrence of any of the following complications: - Bacterial superinfection, - Exacerbation of underlying pulmonary disease, - Cardiovascular and cerebrovascular event, - Respiratory Failure - Clodistridium difficile associated diarrhea. - Other RSV complications If a subject has a complication before the first intake, time will be set to 0. Time to onset of complications will be censored at date of study completion/discontinuation for subjects without complications
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

4.2.6.2. Analysis Methods

<u>The amount of supplemental oxygen</u>

The amount of supplemental oxygen will be listed over time.

<u>Subjects (proportion) who started antibiotic use after the first dose of the study drug</u>

Frequency tabulations will be given for the need for antibiotics related to RSV infection complications, as recorded in the CRF.

Disease status and presence of complications with onset after treatment initiation

Frequency tabulations will be given for any occurrence of RSV complications (Bacterial superinfections, Exacerbations of underlying pulmonary disease, Cardiovascular and cerebrovascular events, Clostridium difficile associated diarrhea, Respiratory failure, Other).

To compare incidence in the presence of complications across treatment groups a stratified (exact) logistic regression model as specified above will be used.

Detailed information on the type of complications, seriousness, severity and outcome will be given as part of the safety analysis (see section 4.3.1).

Hospital readmission for respiratory reasons

Frequency tabulations will be given for Hospitalization readmissions for respiratory reasons.

4.2.7. Exploratory Analyses of Special Interest

4.2.7.1. Relationship between onset of symptoms and viral load

It will be investigated if the onset of symptoms (ie., duration of RSV symptoms before treatment initiation) (days) is predictive of the treatment effect, or in other words if there is evidence of interaction between onset of symptoms and treatment effect.

To investigate this, the following outputs will be provided:

- A trellis plot of the log10 RSV RNA viral load over time by treatment group and day of onset of symptoms showing the individual loads over time (spaghetti plots)
- A trellis plot of the average log10 RSV RNA viral load over time by treatment group and day of onset of symptoms
- A trellis plot of the average log 10 RSV RNA viral load over time by treatment group and onset of symptoms ≤3 days and >3 days (if this cut is sufficiently close to 50% - boundary may be adjusted)

If the data permit the primary endpoint will be fitted using the treatment group by day of onset of symptoms interaction term.

4.3. SAFETY

All safety analyses will be done on the Safety Set.

4.3.1. Adverse Events

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.

Definitions

Treatment-emergent AEs are AEs with onset during the treatment or the follow-up phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-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

Step 1: Allocation of Events to the Phases

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 (treatment-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.

Step 2: Combination of Events

Overlapping/consecutive events are defined as events of the same subject with the same preferred term who have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1) In case a non-active phase (e.g. Screening) is followed by an active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate events.

2) In case overlapping/consecutive events start within a single phase, they are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADAM database but are assigned the same onset, phase, and total duration.

3) In case an active phase is followed by a non-active phase (e.g. Follow-Up), and the overlapping/consecutive events start in both phases, they are allocated to the active phase only and are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADAM database but are assigned the same onset, treatment phase, and total duration.

Remarks:

1) Events can only be combined into one and the same AE if their start and stop dates are complete.

2) In case the completely missing end date is imputed, this date is also considered as a complete date.

3) Time is not considered when determining overlap of events.

4) Adverse events will be reported from the informed consent date on (i.e. in the screening period) until trial termination.

Analysis Methods

A Summary will be provided for the following treatment-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 3-4 AEs.

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

The following adverse events will be tabulated; or listed (in case there are less than 5 events) by subgroups (section 2.5): any AE, any RSV-related complications, any grade 1-2, any grade 3-4 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.

4.3.2. 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.

Unifying multiple laboratory values by standardization:

Since local labs are used, the SI-converted values will be standardized using the following formula and using the phantom laboratory generalized lab norms (GLN) as proposed by Francis Ruvuna, David Flores et all.[13]

$$y = (x - \mathrm{Li}) * \frac{Ucs - Lcs}{Ui - Li} + Lcs$$

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 proposed by Francis Ruvana et all. [13]

The standardized 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). 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) will be determined.

Treatment-emergent definition for toxicity grades and abnormalities

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

Special assessments:

Additional laboratory assessments corresponding to the CRF rash-pages (if any and if applicable) will only be considered in the main analysis if they are provided by the same laboratory vendor as for the main, scheduled assessments.

Otherwise these assessments will only be listed; this also means that these assessments will not be considered in the determination of worst-case per treatment, but toxicity grades or non-graded abnormalities will anyways be determined as and if applicable.

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.

Derivation of GFR (CKD-EPI equation):

Estimated GFR (CKD-EPI equation) will be calculated using the following formula[14]:

GFR(mL/min/1.73 m²) = 141 x minimum(CREAT / K ; 1)α x maximum(CREAT / K ; 1)-1.209 x 0.993Age x (1.018 IF SEX = 'F') x (1.159 IF RACEGR1 = 'BLACK')

Where:
CREAT= Serum Creatinine
Unit CREAT = mg/dL.
Conversion CREAT: mg/dL = umol/L / 88.4
Unit WEIGHT = kg, unit HEIGHT = cm
Use last measurement before intake for weight and height (baseline).
Use age at screening.
K = 0.7 IF SEX= 'F' or 0.9 IF SEX='M'
α = -0.329 IF SEX= 'F' or -0.411 IF SEX='M'

With the following scores:
Grade 0: GFR > 60 mL/min/1.73m2 (grade 0);
Grade 1: 30 mL/min/1.73m2< GFR <=60 mL/min/1.73m2
Grade 2: 15 mL/min/1.73m2< GFR <=30 mL/min/1.73m2
Grade 3: GFR <=15 mL/min/1.73m2

Analysis Methods

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

The number and percentage of subjects will be shown in a cross-tabulation of the toxicity/abnormality post-baseline versus baseline at each scheduled time point.

Additionally, 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 treatment-emergent worst toxicity/abnormality and the cumulative number of subjects per treatment-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.

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

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

4.3.3. Vital Signs

Systolic and Diastolic blood pressure, pulse rate, respiratory rate, tympanic temperature and oxygen saturation will be investigated.

Definitions

The following abnormalities will be defined:

	Vital Signs parameter		
Abnormality Code	Pulse	DBP	SBP
Abnormalities on actual values			
Abnormally low	< 45 bpm	≤ 50 mmHg	≤ 90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	> 140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥ 100 mmHg - < 110 mmHg	≥ 160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥ 110 mmHg	≥ 180 mmHg
Abnormally high	≥ 120 bpm	-	-

Abnormality Code	Respiratory
Abnormalities on actual values	
Normal	< 17 breaths per minute

Abnormality Code	Respiratory
Grade 1 or mild Grade 2 or moderate Grade 3 or severe Grade 4 or potentially life threatening	17-20 breaths per minute 21-25 breaths per minute > 25 breaths per minute intubation-

Abnormality Code	Tympanic Temperature (°C)
Abnormalities on actual values	
Normal Abnormally high	< 37.5 ≥ 37.5

Abnormality Code	Oxygen Saturation (%)
Abnormalities on actual values	
Abnormally low Normal	< 95 ≥ 95

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 treatment-emergent in a particular phase if it is worse than baseline. If baseline is missing, the abnormality is always considered as treatment-emergent. A shift from 'abnormally low' at baseline to 'abnormally high' or 'grade …' post baseline (or vice versa) is also treatment-emergent.

Analysis Methods

Actual values and change from baseline will be summarized by treatment group at each scheduled time point. The number and percentage of will be shown in a cross-tabulation of the toxicity/abnormality post-baseline versus baseline at each scheduled time point.

Additionally, 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 treatment-emergent worst

toxicity/abnormality and the cumulative number of subjects per treatment-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 VS values will be provided.

4.3.4. Physical Examination Findings

Abnormal physical examination will be listed.

4.3.5. Electrocardiogram

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

Definitions

The following abnormalities will be defined:

Abnormality Code	ECG parameter			
	HR	PR	QRS	$QT_{corrected}$
Abnormalities on actual values				
Abnormally low	< 45 bpm	< 110 ms	-	-
Abnormally high	≥120 bpm	> 220 ms	≥ 120 ms	-
Borderline prolonged QT (males)	-	-	-	450 ms < QTc ≤ 480 ms
Borderline prolonged QT (females)	-	-	-	470 ms < QTc ≤ 480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤ 500 ms
Pathologically prolonged QT	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc < 30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤ 60 ms
Abnormally high QTc change	-	-	-	ΔQTc > 60 ms

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 treatment-emergent in a particular phase if it is worse than baseline. If baseline is missing, the abnormality is always considered as treatment-emergent. A

shift from ‘abnormally low’ at baseline to ‘abnormally high’ or ‘grade …’ post baseline (or vice versa) is also treatment-emergent.

Analysis Methods

Actual values and change from baseline will be summarized by treatment group at each scheduled time point. The number and percentage of will be shown in a cross-tabulation of the toxicity/abnormality post-baseline versus baseline at each scheduled time point.

Additionally, 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 treatment-emergent worst toxicity/abnormality and the cumulative number of subjects per treatment-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 tabulation of the worst QT/QTc change versus baseline per treatment per phase will be presented

A listing of abnormal individual subject VS values will be provided.

4.4. VIROLOGY

The emergence of viral resistance will be evaluated by sequencing the RSV polymerase L-gene and other regions (only if no mutations are seen in the L-gene) and looking for changes from baseline, defined as before first dose of ALS-008176. All baseline subject samples will be sequenced to identify pre-existing mutations in their L gene. All post-baseline subject samples that show no viral suppression or viral rebound will be sequenced to identify mutations in the L gene that have occurred after the start of treatment with ALS-008176. Ultra deep sequencing will be used to sequence the L gene for all the subjects. A cut-off of 10-15% will be used to analyze the results. The analysis of the viral resistance data will be documented in a separate clinical virology report.

4.4.1. Analysis Time Points

Virology result will be assigned to the visit windows as described in section 2.1. In addition, the below time points will be considered:

- Baseline (BL): Last available pre-dose time point in the study with sequencing data available
- Time Point of Sequence at End of Treatment (EOTSTPT): Last available post-baseline time point during the treatment phase with sequencing data available
- Time Point of 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

4.4.2. Virus Strain Typing

RSV will be classified into virus strain subtypes based on a duplex qRT-PCR assay.

4.4.2.1. Analysis Methods

The analysis RSV Subtype at baseline will be tabulated and used in the subgroup analyses.

4.4.3. Viral Sequencing

Sequencing of the entire L-gene will be performed to identify pre-existing and/or emerging genetic variations. The frequency of these genetic variations as well as the effect of pre-existing genetic variations on treatment outcome will be explored.

Definitions

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 sequence to be used is a sequence of the L gene of a wild

type strain such as A2 or Long strains in case of comparison to a baseline sample or the baseline sample if wild type when comparing to post-baseline sample.

- **Wild type**: If – at certain position – the amino acid/nucleotide in the subject's virus's sequence matches the reference sequence, that is no genetic variation is present at that position, the virus is considered to be wild type at that position.

- **Emerging genetic variation**: If – at certain position - a genetic variation is absent at Baseline but present at a later time point, the genetic variation considered to be emerging at that time point.

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

When analyzing the pre-existing and/or emerging genetic variations, special attention will be payed to the following (combination of) genetic variations: M628L, A789V, L795I, I796V.

Parameters to analyze

- Number (%) of subjects with a genetic variations at a specific position.

- Number (%) of subjects with a specific genetic variation.

- Number (%) of subjects with a specific genetic variation profile.

- Number (%) of subjects with a number of genetic variations in a specific genetic area of interest.

The following rules will be taken into account to count the number of genetic variations at a specific time point:

- If, at the selected time point, different genetic variations occur/emerge at the same position, this will be counted only once.

- Wild type is never counted as a genetic variation.

- Insertions and deletions will be counted as a separate genetic variations, even if at the same position a genetic variation is already present.

- Subjects with viral sequencing data at the selected time point, but without (emerging) genetic variations of a specific list, should be classified as having zero (emerging) genetic variations for that list.

The focus will be on genetic variations at selected time points, emerging genetic variations and reversion to wild type or baseline state.

4.4.3.1. Analysis Methods

Frequencies and percentages will be presented at the time points specified above for the specified parameters. The denominator is the number of subjects with viral sequencing data, within the region, at the selected time point(s). Results will be shown by time point and region.

4.5. MEDICAL RESOURCE UTILIZATION

Medical resource utilization will be summarized descriptively (number and percentage of subjects) by treatment group at each scheduled time point.

4.6. OTHERS

Relationship between RSV RNA viral load and RSV viral load by qRT-PCR (intubated subjects)

To make a comparison of the RSV RNA viral loads measured in mid-turbinate nasal swabs and endotracheal samples from intubated subjects, scatter plots will be created plotting the RSV RNA viral loads versus the RSV viral load as measured by qRT-PCR of endotracheal samples.

Relationship between viral kinetics and clinical outcome

Kaplan-Meier analysis by quartiles of viral load $AUC_{0\text{-}7\ days}$ for:

- The Length of Hospital Stay/Need (both since treatment initiation and since hospital admission)
- Time to return to pre-RSV functional status (KATZ ADL score)
- Time to clinical stability

A summary table including number of subjects included in the analysis, number of subjects censored, 25^{th} and 75^{th} percentiles and median with 95% confidence intervals based on log-log transformation method, will be presented by quartiles of viral load $AUC_{0\text{-}7\ days}$ parameter.

A Tabulation of the need for additional oxygen supplementation will be presented by quartiles of viral load $AUC_{0\text{-}7\ days}$.

Evolution of diffusing capacity

To explore the evolution of diffusing capacity of the lung for carbon monoxide (DLCO) and spirometry in subjects hospitalized due to RSV infection, descriptive statistics and mean (SE) plots will be shown and the changes from baseline calculated by treatment group.

Impact of ALS-008176 on the infectious viral load

The impact of ALS-008176 on the infectious viral load will be evaluated by descriptive statistics on the RSV infectious viral load as measured using quantitative viral culture (plaque assay).

ATTACHMENT

DMID ADULT TOXICITY GRADES FOR LABORATORY PARAMETERS

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Hemoglobin	g/dL	10.5 – 9.5	<9.5 – 8.0	<8.0 – 6.5	<6.5
Absolute Neutrophil Count	GIGA/L	1.50 – 1.00	<1.00 – 0.75	<0.75 – 0.50	<0.50
Platelets	GIGA/L	<100 – 75	<75 – 50	<50 – 20	<20
WBC, high	GIGA/L	11 – <13	13 – <15	15 – 30	>30
WBC, low	GIGA/L	1 – <4			<1
Fibrinogen, high	mg/dL	400 – 600	>600		
	µmol/L	11.76 – 17.65	>17.65		
Fibrinogen, low	mg/dL	200 – 100	<100 – 50	<50	
	µmol/L	5.88 – 2.94	<2.94 – 1.47	<1.47	
Prothrombin Time		>1.00 x ULN – 1.25 x ULN	>1.25 x ULN – 1.50 x ULN	>1.50 x ULN – 3.00 x ULN	>3.00 x ULN
Activated Partial Thromboplastin Time		>1.00 x ULN – 1.66 x ULN	>1.66 x ULN – 2.33 x ULN	>2.33 x ULN – 3.00 x ULN	>3.00 x ULN
AST		>1.0 x ULN – <2.0 x ULN	2.0 x ULN – <3.0 x ULN	3.0 x ULN – 8.0 x ULN	>8.0 x ULN
ALT		>1.0 x ULN – <2.0 x ULN	2.0 x ULN – <3.0 x ULN	3.0 x ULN – 8.0 x ULN	>8.0 x ULN
GGT		>1.0 x ULN – <2.0 x ULN	2.0 x ULN – <3.0 x ULN	3.0 x ULN – 8.0 x ULN	>8.0 x ULN
Alkaline Phosphatase		>1.0 x ULN – <2.0 x ULN	2.0 x ULN – <3.0 x ULN	3.0 x ULN – 8.0 x ULN	>8.0 x ULN
Amylase		>1.0 x ULN – 1.5 x ULN	>1.5 x ULN – 2.0 x ULN	>2.0 x ULN – 5.0 x ULN	>5.0 x ULN
Lipase		>1.0 x ULN – 1.5 x ULN	>1.5 x ULN – 2.0 x ULN	>2.0 x ULN – 5.0 x ULN	>5.0 x ULN
Hyponatremia	mEq/L mmol/L	135 – 130	<130 – 123	<123 – 116	<116
Hypernatremia	mEq/L mmol/L	146 – 150	>150 – 157	>157 – 165	>165
Hypokalemia	mEq/L mmol/L	3.4 – 3.0	<3.0 – 2.5	<2.5 – 2.0	<2.0
Hyperkalemia	mEq/L mmol/L	5.6 – 6.0	>6.0 – 6.5	>6.5 – 7.0	>7.0
Hypoalbuminemia	g/dL	<LLN – 3	<3 – 2	<2	
Hypoglycemia	mg/dL	64 – 55	<55 – 40	<40 – 30	<30
	mmol/L	3.55 –3.05	<3.05 – 2.22	<2.22 – 1.67	<1.67
Hyperglycemia	mg/dL	116 – 160	>160 – 250	>250 – 500	>500
	mmol/L	6.44 – 8.88	>8.88 – 13.88	>13.88 – 27.75	>27.75
Hypocalcemia (corr. for albumin)	mg/dL	8.4 – 7.8	<7.8 – 7.0	<7.0 – 6.1	<6.1
	mmol/L	2.10 – 1.95	<1.95 – 1.75	<1.75 – 1.52	<1.52
Hypercalcemia (corr. for albumin)	mg/dL	10.6 – 11.5	>11.5 – 12.5	>12.5 – 13.5	>13.5
	mmol/L	2.64 – 2.87	>2.87 – 3.12	>3.12 –3.37	>3.37
Hypomagnesemia	mEq/L	1.4 – 1.2	<1.2 – 0.9	<0.9 – 0.6	<0.6
	mmol/L	0.70 – 0.60	<0.60 – 0.45	<0.45 – 0.30	<0.30
Hypophosphatemia	mg/dL	2.4 – 2.0	<2.0 – 1.5	<1.5 – 1.0	<1.0
	mmol/L	0.77 – 0.65	<0.65 – 0.48	<0.48 – 0.32	<0.32
Hyperbilirubinemia (TB)		>1.0 x ULN – <1.5 x ULN	1.5 x ULN – <2.0 x ULN	2.0 x ULN – 3.0 x ULN	>3.0 x ULN

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
BUN		>1.24 x ULN – 2.50 x ULN	>2.50 x ULN – 5.00 x ULN	>5.00 x ULN – 10.00 x ULN	>10.00 x ULN
Hyperuricemia (uric acid)	mg/dL	7.5 – 10.0	>10.0 – 12.0	>12.0 – 15.0	>15.0
	µmol/L	446 – 595	>595 – 714	>714 – 892	>892
Creatinine		>1.0 x ULN – 1.5 x ULN	>1.5 x ULN – 3.0 x ULN	>3.0 x ULN – 6.0 x ULN	>6.0 x ULN
Hypertriglyceridemia		>1.0 x ULN – <2.5 x ULN	2.5 x ULN – 5.0 x ULN	>5.0 x ULN – 10.0 x ULN	>10.0 x ULN

ULN = Upper Limit of Normal LLN = Lower Limit of Normal

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