

CONFIDENTIAL



# **STATISTICAL ANALYSIS PLAN**

## **ALX0171-C201**

**A Randomized, Double-Blind, Placebo-Controlled, Multicenter  
Dose-Ranging Study of ALX-0171 in Infants and Young Children  
Hospitalized for Respiratory Syncytial Virus Lower Respiratory  
Tract Infection.**

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## 1 LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BPM	Beats per minute
BQL	Below the limit of quantification
CI	Confidence Interval
CM	Concomitant medication
CRO	Contract research organization
CSP	Clinical study protocol
DAP	Data analysis plan
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
FDA	Food & Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GSS	Global Severity Score
HFOT	High flow oxygen therapy
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-treat
i.v.	Intravenous
IWRS/IVRS	Interactive web/voice response system
KL-6	Krebs von den Lungen
KM	Kaplan-Meier
LBA	Ligand binding assay
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LRTI	Lower respiratory tract infection
LSLV	Last visit of the last subject
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NAb	Neutralizing anti-drug antibodies

O <sub>2</sub>	Oxygen
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred Term
Pre-Ab	Pre-existing antibodies
qPCR	Quantitative polymerase chain reaction
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
RACS	Respiratory Assessment Change Score
RDAI	Respiratory Distress Assessment Instrument
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SAP	Statistical analysis plan
SOC	System Organ Class
SpO <sub>2</sub>	Peripheral capillary oxygen saturation
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
VAS	Visual Analogue Scale
WHO	World Health Organization



## 2 INTRODUCTION

This statistical analysis plan (SAP) contains a technical and detailed elaboration of the principal features of the analyses described in the clinical study protocol (CSP) for the ALX0171-C201 study, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

ALX-0171 is a therapeutic protein (Nanobody) that is currently being developed for the treatment of Respiratory syncytial virus lower respiratory tract infection (RSV LRTI). As a respiratory virus, RSV may present as an upper respiratory tract infection (including rhinitis, otitis media and pharyngitis), or, as is more often the case in infants and young children, as a LRTI, (including acute bronchiolitis and/or broncho-pneumonia). RSV LRTI is a leading cause of bronchiolitis in infants and results in over 3 million hospitalizations worldwide per year. RSV LRTI results in hospitalization of about 3% of RSV-infected infants less than 1 year old, and about 0.5% of RSV-infected children aged between 1 and 2 years [1, 2]. Since there are no adequate medications available for treatment of RSV infection, the standard of care for hospitalized infants is mostly supportive (e.g., fluid/feed supplementation, observation, and respiratory support as needed) [1, 3, 4].

ALX-0171 is an antiviral treatment and is intended to neutralize RSV (thereby inhibiting viral infectivity). The antiviral effect of ALX-0171 is expected to provide rapid control of the infection, thereby reducing the intensity and duration of severe disease. ALX-0171 was shown to be highly effective in nonclinical in vitro and in vivo model systems, including RSV-infected cotton rats and neonatal lambs. Results from these studies demonstrate a beneficial effect with regard to viral load, inflammatory signs, and/or symptoms and signs of RSV infection. The studies in RSV-infected neonatal lambs provided proof-of-concept for therapeutic intervention with a 3-day treatment course of ALX-0171.

In the first pediatric study, inhaled ALX-0171 demonstrated pharmacological effect in a relevant clinical setting by an immediate impact on viral titers in nasal swab specimen. Analysis of a composite of clinical parameters, the Global Severity Score, led to an encouraging initial indication of a therapeutic effect for infants treated with ALX-0171 and warrants further assessment of this potential clinical benefit in a larger study.

The nonclinical and clinical studies performed so far did not reveal clinically meaningful risks for administration of ALX-0171 to pediatric subjects. The results in representative nonclinical models, together with those obtained in first-in-infant Study ALX0171-C104, indicate that ALX-0171 may provide an opportunity for therapeutic intervention in established RSV LRTI.

The doses that are administered to subjects in Study ALX0171-C201 are estimated to achieve concentrations at which antiviral and clinical activity can be expected while appropriate safety margins are respected. Regular review of cumulative unblinded safety data by the Independent Data Monitoring Committee (IDMC), after completion of treatment or discontinuation of treatment of last subject in each safety cohort and after 72 subjects received

treatment during the parallel cohort, together with the predefined stopping criteria defined in the CSP section 3.1.1 , enable adequate safety follow-up throughout the study.

### 3 STUDY OBJECTIVES

#### 3.1 Primary Objective

To evaluate the anti-viral effect and safety of different doses of inhaled ALX-0171 in subjects hospitalized for RSV LRTI.

#### 3.2 Secondary Objectives

To evaluate the clinical activity, pharmacokinetic (PK) properties, pharmacodynamic (PD) effect and immunogenicity of different doses of inhaled ALX-0171.

### 4 STUDY DESIGN

#### 4.1 Overall study design

This is a Phase IIb randomized, double-blind, placebo-controlled, international, multicenter dose-ranging study. Study drug is administered along with standard of care treatment, which is determined by the Investigator (or his/her designee) according to institutional practice.

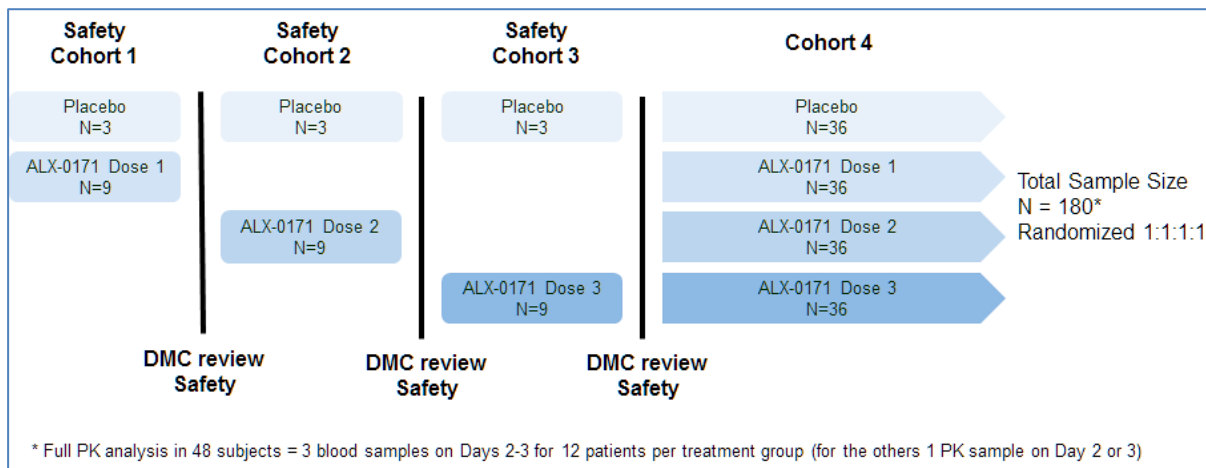
Three dose levels of ALX0171 are being evaluated:

- Dose 1: target dose of 3.0 mg/kg
- Dose 2: target dose of 6.0 mg/kg
- Dose 3: target dose of 9.0 mg/kg

Study drug is administered once daily for 3 consecutive days. The 3-day treatment period is expected to bridge the time needed for the body to mount an effective immune response.

The study plans to enroll approximately 180 infants and young children (aged 28 days to < 2 years) who are diagnosed with and hospitalized for RSV LRTI.

The study consists of a sequential part followed by a parallel part (Figure 1).



**Figure 1: Overview of study design**

In safety cohorts 1 to 3, sequential dose escalation is used to enable appropriate safety follow-up. Each of the 3 safety cohorts consists of 12 subjects (N=36 in total) randomized 3:1 to ALX-0171 (N=9) or placebo (N=3).

In addition to the individual discontinuation criteria (see CSP section 3.2.3), criteria for stopping or pausing recruitment in a safety cohort and criteria to stop dose escalation will apply in the sequential part of the study (see CSP section 3.1.1). These criteria will also be used to decide on the doses taken forward into Cohort 4 (i.e., parallel part of the study).

In addition to these dose stopping criteria, cumulative unblinded safety data is reviewed by an IDMC consisting of an independent group of 3 clinical experts and a statistician, not participating in the study. The IDMC advises the sponsor on proceeding to the next cohort and which planned dose levels can be taken forward in the parallel cohort.

Since no stopping criteria have been met during the sequential part and the IDMC issued a positive recommendation after each safety cohort, the remaining 144 subjects (i.e., Cohort 4) were randomly assigned in a 1:1:1:1 ratio to one of following treatment groups, yielding an overall randomization ratio of 3:1 active to placebo.

- ALX-0171 dose 3.0mg/kg
- ALX-0171 dose 6.0mg/kg
- ALX-0171 dose 9.0mg/kg
- Placebo

During the parallel part of the study, an IDMC review took place after 72 subjects received treatment in the parallel part.

The Placebo group will serve as comparator group for the 3 ALX-0171 treatment groups. To achieve double-blinding across the different groups, each dose is administered as two serial nebulizations. These two nebulizations consists either of two nebulizations of ALX-0171, or

one of ALX-0171 and one of placebo, or two nebulizations of placebo depending on the assigned treatment group.

Subjects are screened as soon as possible after arrival to the hospital/emergency unit and randomized shortly thereafter (within 24 hours after arrival). Study drug administration starts with a maximum time interval of 3 hours following randomization. Subsequent doses of study drug are administered at 24-hour intervals ( $\pm 4$  hours) relative to the first dose. On the first 2 dosing days, inpatient hospital stay is required. Provided that the clinical response criteria have been met, discharge from the hospital can take place per protocol at the Investigator's discretion from dosing Day 2 onwards after all required assessments of the 5 hours ( $\pm 1$  hour) post-dose time point have been completed. Subjects discharged after the second dose must return to the hospital for the third study drug administration (to be administered  $48 \pm 4$  hours after the first dose by the appropriately trained study personnel), and be monitored for a 2-3 hour pre-dose and post-dose period (depending on the used protocol version, please see 19.1 for Time and events under different protocol versions) . Subjects who are not discharged from the hospital after completion or premature discontinuation of study drug enter an in-hospital post-treatment period with assessments in the morning and evening. A Follow-Up (FU) visit is scheduled on Day 14 ( $\pm 2$  days), and an End of Study (EOS) visit on Day 28 ( $\pm 2$  days). A detailed description of the scheduled assessments and their timing can be found in Section 19.1.

## 4.2 Sample size

With 45 subjects per arm, 85% power is achieved to detect a 50% reduction in median time-to-BQL (0.5 day with ALX-0171 versus 1 day with placebo) for the plaque assay using a two-sided log-rank test at significance level of 0.05. For each comparison of the ALX-0171 treatment groups with placebo, a significance level of 0.05 is assumed. For multiple pairwise comparisons, the family-wise error rate is controlled at 5% through the closed testing principle, where the comparison of the lower dose of ALX-0171 to placebo is only performed if the comparison of the higher dose of ALX-0171 to placebo is significant. The sample size also incorporates a 15% drop-out rate. With this sample size, a power of 80% is achieved to detect a difference of 2 points in the mean change from baseline (to Day 2 post-dose) on the Global Severity Score for each of the ALX-0171 treatment groups to placebo. This is based on a two-sided t-test with a significance level of 0.05 and assuming a common standard deviation of 3.2 in each group.

## 4.3 Study Endpoints

### 4.3.1 Primary Endpoint

Anti-viral effect as measured by the time needed for the viral load to drop below the plaque assay quantification limit (time-to-BQL) in nasal mid-turbinate swab specimens.

### 4.3.2 Secondary Endpoints

- Safety assessment (assessed by physical examination, AEs, laboratory assessments and vital signs) of different doses of ALX-0171
- Change from baseline in Global Severity Score
- Time to clinical response: defined as the time between first administration of study drug and achieving adequate oxygen saturation and oral feeding
- PK properties of ALX-0171
- Viral load profile over time in nasal swab specimens (RT-qPCR and plaque assay)
- Evaluation of serum anti-drug antibodies (ADA)

### 4.3.3 Other Endpoints

- Evolution over time in clinical symptoms (SpO<sub>2</sub>, feeding, respiratory rate, wheezing, cough, respiratory muscle retractions, and general appearance)
- Evolution over time in RDAI, RACS
- Length of hospital stay defined as time between admission and discharge
- Length of hospital stay for RSV defined as time between admission and discharge excluding prolongation due to SAE other than RSV worsening
- Time between first study drug administration and discharge
- Duration of severe disease, defined as time from admission to hospital to time of clinical response
- Duration of supplemental oxygen therapy
- Duration of feeding support
- Initiation of invasive and non-invasive ventilation and duration of respiratory support
- Transfer to ICU and duration of ICU stay
- Parent(s)/Caregiver(s) assessment of the clinical condition of the subject
- Evolution of serum biomarker over time

## 5 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

### 5.1 Analysis populations

The following populations will be considered for analysis:

#### 5.1.1 All Screened Population

The All Screened population consists of all subjects that were screened during the trial (i.e, subjects with an informed consent form (ICF) (RSV test informed consent and/or study informed consent) signed by parent(s)/legal guardian(s) or legally acceptable representative(s).

#### 5.1.2 Intent-to-treat (ITT) Population

The ITT population consists of all randomized subjects.

### 5.1.3 Modified Intent-to-treat (mITT) Population

The mITT population consists of all randomized subjects who received at least 1 administration of study drug. When using this population, the subjects will be classified as randomized (i.e., using the treatment to which the subject was randomized). This will be the primary study population for the analysis of baseline characteristics, efficacy and pharmacodynamic data.

### 5.1.4 RSV Infected population

The RSV Infected population consists of all randomized subjects with RSV infection, as confirmed by RT-qPCR (hVIVO quantitative PCR assay) on Day 1 (pre- or post-dose), who received at least 1 administration of study drug. Subjects will be classified as randomized when using this population. Dedicated outputs on the RSV infected population will only be created if this population differs from the mITT population.

### 5.1.5 Safety Population

The safety population consists of all subjects who received at least 1 administration of study drug. When using this population, the subjects will be classified as treated (i.e., using the treatment that the subject actually received, see section 5.2). This will be the primary population for the analysis of prior/concomitant medication, exposure, safety and immunogenicity data

### 5.1.6 Per Protocol (PP) Population

The PP population consists of a subset of the RSV Infected population, and excludes those subjects who have had a major protocol deviation that could potentially impact the primary efficacy endpoint (please refer to 19.3 Appendix C for more details). The subjects will be classified as treated when using this population.

### 5.1.7 Extensive PK Population

The Extensive PK population consists of subjects with consent for extensive PK assessments who have 3 PK assessments done.

## 5.2 Treatment Regimen

For baseline characteristics, efficacy parameters and pharmacodynamics data, the treatment group as assigned by the randomization system will be used in the analysis (i.e., as-randomized analysis).

For prior/concomitant medication, exposure, safety and immunogenicity parameters, the treatment that was actually administered to the subject will be applied in the analysis (i.e., as-treated analysis).

In case a subject in the Placebo group received active study medication, the subject will be assigned to the lowest active treatment group the subject received as actual treatment and analyzed accordingly for the as-treated part of the analysis.

For subjects who received active study medication from more than one active treatment group, the actual treatment group will be set equal to the treatment group assigned by the randomization system, if one of the active doses received is the same as the treatment group the subject has been randomized to; otherwise the actual treatment group will be set to the lowest active treatment group the subject received for the as-treated part of the analysis.

For subjects randomized to active study medication who only received placebo, the actual treatment group will be set to placebo.

Differences between as-treated and as-randomized will be flagged in the listing on subject allocation.

### 5.3 Key Definitions

#### 5.3.1 Definition of baseline

Baseline is defined as the last non-missing assessment before first administration of study drug.

#### 5.3.2 Change from baseline

Absolute change from baseline will be calculated for all post-baseline time-points as:  
[Change from baseline at timepoint t]=[actual value at t] – [Baseline value]

Percent change from baseline will be calculated as:  
[% change from baseline at timepoint t]=[[[actual value at t] – [baseline value]] / [baseline value]]\*100

If baseline value is missing both change from baseline and percent change from baseline will be set to missing.

#### 5.3.3 Imputation of missing data

##### 5.3.3.1 Safety data

Analysis of safety data will be done on observed cases only.

##### 5.3.3.2 Efficacy data: Last observation carried forward (LOCF)

For a large part the efficacy analysis will be done on observed cases, only a limited number of missing data will be imputed (please refer to Section 14.2 for more details). For endpoints with an LOCF imputation, no observed case analysis will be performed.



For LOCF imputation, missing post-baseline values are imputed by the last nonmissing preceding value (including the baseline value). Baseline values are not imputed because per definition, it is the last available pre-dose value. See example below:

	Baseline	...	Day 1	Day 2	Day 3	Day 4
Case 1	Value1	...	Value2	Missing: imputed by Value 2	Missing: imputed by Value 2	Missing: imputed by Value 2
Case 2	Missing: not imputed	...	Value2	Value3	Value4	Missing: imputed by Value 4

### 5.3.4 Time to event

Time to event is defined as the time from the reference point (mostly first dosing) to the first occurrence of the event under consideration.

The censoring mechanism will be described for each time-to-event endpoint separately.

## 5.4 General Methods

### 5.4.1 Summary statistics

For continuous variables, descriptive statistics will be presented. Descriptive statistics will include the number of non-missing data points (n), the arithmetic mean, the standard deviation (SD) (for baseline summaries) and standard error (SE) (for post-baseline or change from baseline summaries), the median, minimum and maximum.

Descriptive statistics of the baseline global severity score (GSS) will additionally include quartiles (Q1 and Q3).

Descriptive statistics of the pharmacodynamic parameter Krebs von den Lungen-6 (KL-6) and of the study drug concentrations by ADA and Nab subject classifications will additionally include 5% and 95% percentiles, geometric mean, geometric SD and coefficient of variation (CV)% of arithmetic mean.

For categorical variables, frequency tabulations will be presented, consisting of frequency counts and percentages. Missing observations (counts) will be tabulated as a separate category but not taken into account for calculating percentages (denominator for percentages is total of non-missing observations within the group). Both zero count categories (rows) within a parameter as well as treatment groups without counts/events (columns) will be shown in the tables .



#### 5.4.2 Graphical representation

For graphs showing mean values, standard error bars will be shown.

#### 5.4.3 Reporting precision

Reporting precision will be driven by the number of significant digits of the original result, unless specifically mentioned.

#### 5.4.4 Statistical significance

For inferential testing, p-values will be referenced against a significance level of 5% ( $\alpha=0.05$ ) unless specified otherwise.

#### 5.4.5 Handling of outliers

No special data handling is foreseen for outlier values.

#### 5.4.6 Totals over groups

Grand total, pooling all subjects, will be displayed only in the tables on subject disposition, demographic and baseline characteristics. A total over all active groups (ALX-0171 Total) will be shown for all safety and efficacy tables unless mentioned otherwise in the description. Outputs will not be presented separately by cohort.

### 5.5 Software and validation model

#### 5.5.1 Software

SAS version 9.2 will be used for programming.

#### 5.5.2 Validation model

Currently valid ████████ STAT SOPs will be followed.

The ADaM datasets and tables related to primary and secondary efficacy endpoints will be validated through independent programming;

Apart from primary and secondary efficacy endpoints all other ADaM datasets, tables, listings and figures will be validated by review of the output, source code and program log by an independent person (i.e., somebody different from the developer).

## 6 GENERAL CHARACTERISTICS

A detailed list of tables and listings can be found in Section 16.1 and Section 18.1, respectively.

## 6.1 Subject Disposition

Subject disposition will be listed and summarized. The summary tables will be presented by treatment group and overall for the all screened population. This includes the number and percentage of subjects in each of the analysis populations defined in Section 5.1. The number and percentage of subjects by country and site will be summarized by treatment group and overall for the ITT population. The number and percentage of subjects who completed the study drug/trial and who prematurely discontinued will also be summarized for ITT population, along with the primary reasons for discontinuation of study drug/trial.

The number and percentage of screen failures will also be summarized along with the primary reason for screen failure.

## 6.2 Protocol Deviations and Eligibility Criteria

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Major protocol deviations concern criteria and disease characteristics that are critical to define the study population and criteria that determine or influence clinical endpoints or criteria that may cause immediate hazard to the subjects (impact on subjects' rights, safety or well-being) or increase the risk to subjects.

The list of (potentially) major protocol deviations will be reviewed by the sponsor and finalized prior to database lock. Detailed information can be found in the trial specific major protocol deviation criteria list.

Major protocol deviations will be tabulated for the mITT population according to their category:

- Selection criteria not met
- Subject not withdrawn as per protocol
- Treatment non-compliance
- Prohibited concomitant medication
- Efficacy assessment deviation
- Safety assessment deviation
- Other

Additionally, major protocol deviations will be listed. Subjects without any major protocol deviation will not be included in the listing.

Subjects with major protocol deviations that could potentially impact the primary efficacy endpoint will be excluded from the PP Population. A detailed list of protocol deviations that will lead to exclusion from the PP population can be found in Appendix C: Major Protocol deviation criteria with potential impact on primary efficacy.

The major protocol deviations that lead to exclusion from the Per Protocol population will be tabulated for the RSV Infected population.

### 6.3 Demographic and Baseline Characteristics

The following demographic and baseline disease characteristics will be summarized descriptively (as defined in Section 5.4) using the following analysis populations:

- Modified intent-to-treat population
- RSV Infected population
- Per Protocol population

Additionally demographic and baseline disease characteristics will be listed

#### Demographic parameters:

- Gender at birth: male / female
- Age at the moment of signing the ICF (months): the age is not recalculated when already available in the database. Following rounding to a fraction of 0.25 will be applied (if calculated):
  - $\leq 1$  month : 1.00 months
  - x months+0-6 days : x.00 months
  - x months+7-13 days : x.25 months
  - x months+14-20 days : x.50 months
  - x months+21-30 days : x.75 months
- Age category: <6 months, 6 - <12 months and  $\geq 12$  months
- Gestational age (weeks)
- Race: not allowed to ask per local regulations / white / black or African American / Asian / American Indian or Alaska native / native Hawaiian or other Pacific islander / other
- Ethnicity: not allowed to ask per local regulations / Hispanic or Latino / non-Hispanic or non-Latino
- History of atopy in 1<sup>st</sup> grade family
- Exposure to tobacco
- Exposure to pets
- Breastfed
- Height (cm)
- Weight (kg)
- Weight category (3.0 to <4.0, 4.0 to <5.0, 5.0 to <7.0, 7.0 to <10.0, 10.0 to <12.0, 12.0 to <15.0 kg)

#### Baseline disease characteristics:

- RSV diagnosis (test method, test result)
- RSV signs and symptoms
- Number of days between symptom onset and first dose of study drug
- RSV severity criteria :
  - Number of subjects with inadequate oral feeding,
  - Number of subjects with inadequate oxygen saturation,

- Number of subjects with respiratory distress,
  - Number of subjects with inadequate feeding and inadequate oxygen saturation,
  - Number of subjects with inadequate feeding, inadequate oxygen saturation and respiratory distress.
- 
- Global Severity Score (GSS)
  - RDAI score
  - Number of subjects on oxygen supplementation

A listing for above mentioned demographic parameters and another for these baseline characteristics related parameters will be produced for all subjects in the mITT population.

The 19 viral screening tests performed at Baseline (please refer to 19.4 Appendix D for the list of viruses/bacteria tested) and their result (positive or negative) will be tabulated together with general subgroup classification (RSV only or Co-Infected) and will also be listed individually.

#### **6.4 Medical History**

Medical history will be tabulated by (sub)category and additionally listed for the mITT population.

#### **6.5 Prior and Concomitant Medications**

All prior and concomitant therapies will be coded using the latest WHO-DRUG version, and classified using Anatomical therapeutic chemical classification system (ATC level 4 class).

Medications will be classified as prior or concomitant, as reported in the CRF. Prior medications are medications which ended before the signing of informed consent. Concomitant medications are medications which are ongoing at signing of informed consent or which started after the signing of informed consent.

Prior and concomitant therapies will be tabulated by ATC level 4 class and generic term using the safety population. Multiple records of the same generic term for the same subject and ATC level 4 class will be counted only once. The table will therefore present subjects, not occurrences. The tables will be sorted by decreasing frequency (overall). Additionally, all information will be listed.

#### **6.6 Exposure to Study Medication**

The number of subjects in the safety population receiving study medication by day (and nebulization) will be tabulated.

Additionally, exposure and compliance related data including administration information like:

- Administration fully done
- Inhalation period interrupted
- Contact with the face mask
- Resistance to study drug administration
- Crying during nebulization
- Problem occurrence during use of the device

will be tabulated per each nebulization and listed together with any comments on administration events.

The study treatment compliance will also be summarized.

Compliance will be calculated as:

$$\text{Compliance (\%)} = [(\text{number of actual doses})/(\text{number of planned doses})] * 100$$

Any nebulization that was initiated will be considered as actual dose, even if it was not fully administered. Calculation of planned doses will take into account the on-treatment period (up to discontinuation of the subject).

## 7 EFFICACY

A detailed list of tables, listings and figures can be found in Section 16.2, Section 17.2, and Section 18.2 respectively.

### 7.1 Primary Efficacy Endpoint Evaluation

The primary endpoint for this trial is the time needed for the viral load to drop below the plaque assay quantification limit (time-to-BQL) in nasal mid-turbinate swab specimens. Time to BQL is defined as the time from the reference point (first dosing) to the first occurrence of a value below the limit of quantification, provided the next measured value is below the limit as well. The time to event for subjects with missing data and/or who did not reach BQL during the trial will be censored at the last nonmissing viral load assessment .

The time-to-BQL will be compared between each of the ALX-0171 treatment groups and the combined placebo group using a log-rank test. The null hypothesis of this test assumes no difference in time-to-BQL between Placebo and ALX-0171 treated subjects. The tests will be performed in a sequential way to preserve the family-wise error rate at 0.05. Specifically, dose 3 (highest dose) of ALX-0171 will first be tested against the combined placebo group at the 0.05 significance level. Dose 2 of ALX-0171 will only be compared to placebo at the 0.05 significance level if the comparison of dose 3 with placebo is significant. Consequently, dose 1 of ALX-0171 will only be compared to placebo at the 0.05 significance level if the comparison of dose 2 of ALX-0171 with placebo is significant. The primary efficacy endpoint will be evaluated using the mITT population.

The logrank test is based on the assumptions that censoring is unrelated to prognosis and the event probabilities are the same for subjects recruited early and late in the study. Kaplan-Meier (KM) estimates on time-to-BQL will be tabulated (Median, 25<sup>th</sup>, 75<sup>th</sup> percentile with confidence interval and general information on censoring) and a graph of the Kaplan-Meier survival curve will be presented.

The data will also be analyzed using a Cox proportional hazards regression model with time to BQL as dependent variable, and treatment group, viral load at baseline and co-infected subject group as independent variables. The hazard ratio (HR) from the Cox model along with the 95% CI will be reported. This analysis will only be performed for the treatment groups where the comparison was significant as analyzed by the log rank test.

For sensitivity analyses, the primary endpoint will also be evaluated using:

- the RSV Infected population
- the Per Protocol population.

## 7.2 Secondary Efficacy Endpoints Evaluation

### 7.2.1 Key Secondary Endpoint: Global Severity Score (GSS)

- As key secondary endpoint, a formal comparison for change from baseline in GSS (see Section 14.3.2 for computation details) to Day 2, 5 hours post dose will be performed using a contrast analysis on a longitudinal mixed model with random factor subject and fixed effects baseline value, treatment group and timepoint including the treatment-by-timepoint interaction term. All data up to and including Day 3 will be used in the longitudinal mixed model. The Kenward-Roger approximation of degrees of freedom will be used. The model will initially be fitted using an unstructured variance-covariance matrix. In case of non-convergence this may be replaced with a autoregressive variance covariance matrix with heterogeneous variance (ARH) to achieve convergence of the model. The individual pair-wise comparisons will be reported. No formal multiplicity correction will be performed. This comparison will be performed for mITT, RSV infected and PP population.
- For GSS and each of the GSS subitems where GSS is not missing, descriptive statistics will be provided for the actual values and the change from baseline for all planned timepoints. In addition to these planned timepoints, a separate timepoint (Day of hospital discharge) will be created using the last value on the date of discharge from the hospital for GSS summary tables.
- The mean GSS  $\pm$  SE will presented graphically over time (excluding the in-hospital post-treatment assessments), as well as the mean change from baseline  $\pm$  SE. Two bar charts will be provided. One bar chart will present the mean GSS and contributing subitems at all timepoints up to Day 3, 2 hours post dose. The second bar chart will present the mean GSS and contributing subitems over the whole study period (excluding the in-hospital post-treatment timepoints), but will for the first 3 days only include the pre-dose assessments.

Descriptive statistics and figures will be performed on both mITT and RSV infected population

## 7.2.2 Other Secondary Endpoints

### 7.2.2.1 Clinical Response

Clinical response is defined as achieving adequate oxygen saturation and adequate oral feeding. The time to clinical response (hours), defined as the time between the first study drug administration and achieving clinical response, will be summarized using KM estimates and presented graphically. Subjects who already achieved clinical response before the start of dosing, will be excluded from the analysis.

The time to achieving adequate oxygen saturation and the time to achieving adequate oral feeding will be summarized similarly. Subjects who already achieved adequate oxygen saturation or already achieved adequate oral feeding before the start of dosing, will be excluded from the analysis, respectively.

The time to event for subjects with missing data and/or who did not reach the clinical response for oxygen saturation and oral feeding during the trial will be censored at the last nonmissing assessment of blood oxygen level in the vital signs domain (VSTESTCD=OXYSAT) or assessment of adequate oral feeding (DCTESTCD=FEDADQ) If only one condition is reached, then the time to clinical response is censored at the last non missing assessment of the condition which was not met. The same rule will be applied for the time to achieving adequate oxygen saturation and the time to achieving adequate oral feeding.

### 7.2.2.2 Viral Load

In this study, viral titers are measured using the plaque assay for the primary endpoint and by RT-qPCR for the secondary endpoint(s). As secondary endpoint, the time to BQL using RT-qPCR will be summarized using KM estimates. No p-values will be provided.

The time to undetectability (hours) defined as the time from the first study drug administration to first occurrence of viral titer below the lower limit of quantification (LLOQ) and target not detected, provided the next measured value is below the quantification limit and undetected as well, will be summarized using KM estimates, based on the plaque assay and RT-qPCR. The time to event for subjects with missing data and/or who did not reach undetectability during the trial will be censored at the last nonmissing viral load assessment .

In addition, the number and percentage of subjects that have viral titers BQL (for both virus and RNA) and with undetectable viral load will be tabulated over time.

Viral load measured by plaque forming unit assay (log<sub>10</sub> PFU/mL) and by RT-qPCR (log<sub>10</sub> viral copies/mL) will be summarized as continuous variables:

- Viral load (actual values and absolute change from baseline) in nasal swab specimens (RT-qPCR and plaque assay) will be presented using descriptive statistics (see section 5.4.1) over time. Viral load will also be presented graphically by plots describing the mean over time (+SE).



For the summary statistics, samples that are below the lower limit of quantification (LLOQ) (i.e. BQL) will be assigned a value of half the LLOQ level.

- Time weighted average change from baseline up to Day 3 and Day 14 (both virus and RNA) (see section 14.3.1 for calculation method).

Viral load analysis will be performed on mITT and RSV infected population

### 7.2.2.3 PK

Individual study drug concentrations, actual sampling time and actual sampling times relative to second study drug administration time (in hours) will be listed. Drug concentrations with actual sampling times out of time windows per study protocol, will be flagged.

The other analyses on pharmacokinetic data (e.g the modelling) are outside the scope of this SAP and will be described in a separate Data Analysis Plan (DAP).

## 7.3 Other Efficacy Analyses

- Evolution over time in clinical symptoms will be evaluated. The body temperature and respiratory rate (actual values, change from baseline and percent change from baseline) will be summarized descriptively over time. Frequency tabulations will be provided to summarize the feeding, respiratory distress parameters (Wheezing (during inspiration/expiration), lung fields affected, crackles/crepitations, respiratory muscle retractorations (supravascular, intercostal and subcostal) , cough and general appearance of the subject over time. Respiratory rate and body temperature will also be presented graphically in mean  $\pm$  SE plots (excluding the in-hospital post-treatment timepoints).
- Respiratory Distress Assessment Instrument (RDAI) and Respiratory Change Score (RACS) will be calculated (see Section 14.2.3 and 14.2.4 for calculation method, respectively) . Actual values (RDAI, RACS) and changes from baseline (RDAI) will be summarized over time using descriptive statistics (both subitem and totals). RDAI, change from baseline in RDAI and RACS will also be presented graphically in mean  $\pm$  SE plots (excluding the in-hospital post-treatment timepoints). Similar to GSS, bar charts will be generated for RDAI to visualize contributing subitems.
- Length of hospital stay (in days – see section 14.2.9 for calculation method) defined as time between admission and discharge for the initial hospitalization will be summarized as descriptive statistics and using KM estimates. In case of missing discharge information the subject will be censored on date(time) of trial termination.
- The time between first study drug administration and discharge (in days) for the initial hospitalization will be summarized as descriptive statistics and using KM estimates. In case of missing discharge information the subject will be censored on date(time) of trial termination.



- Length of hospital stay for RSV: The time between hospital admission and discharge (in days) excluding prolongation due to SAE other than RSV worsening. Time will be summarized as descriptive statistics and using KM estimates. In case of missing discharge information the subject will be censored on date(time) of trial termination. If needed time will be imputed with 18u00 (see section 14.2.10 for calculation details).
- Duration of severe disease (in hours) defined as the time between hospital admission and achieving clinical response will be summarized using KM estimates. The time to event for subjects with missing data and/or who did not reach the clinical response during the trial will be censored at the last nonmissing assessment of blood oxygen level in the vital signs domain (VSTESTCD=OXYSAT) or assessment of adequate oral feeding (DCTESTCD=FEDADQ).
- A cross-tabulation will present the proportion of subjects on oxygen supplementation at baseline versus post-baseline (i.e., any time between first dose date/time and end of study) per treatment group. Additionally, duration of supplemental oxygen therapy (in hours) defined as total time of reported oxygen supply will be calculated based on concomitant medication (CM) records with coded term 'Oxygen' and summarized descriptively. In case of missing CM information a worst case imputation will be applied (see section 14.2.6 for calculation and imputation rules).
- A cross-tabulation will present the proportion of subjects on feeding support at baseline versus post-baseline (i.e., any time between first dose date/time and end of study) per treatment group. Additionally, duration of feeding support (in hours) defined as total time of reported feeding support will be calculated based on concomitant medication records. In case of missing CM information a worst case imputation will be applied (see section 14.2.7 for calculation and imputation rules).
- Incidence of initiation of invasive and non-invasive ventilation (continuous positive airway pressure, bilevel positive airway pressure and high flow ventilation) as well as incidence of apnea will be tabulated. Additionally, duration of invasive and non-invasive ventilation will be summarized descriptively (in hours - see Section 14.2.8 for calculation method).
- The number and percentage of subjects transferred to ICU and duration of ICU stay (in days – see section 14.2.9 for calculation method) will be summarized using descriptive statistics
- Parent(s)/Caregiver(s) diary assessment will be reported as
  - Frequency tabulation over time (condition as before RSV, severity of cough, severity trouble breathing and severity wheezing).
  - Time to 'Condition as before RSV' will be summarized using KM estimates. Time to will be calculated as the time between first dose and the first occurrence of condition as before RSV. The time to event for subjects with missing data and/or who did not reach event during the trial will be censored at the last nonmissing assessment.

- Based on the individual items collected in the diary, a respiratory symptoms score will be calculated. Respiratory symptoms score will be summarized using descriptive statistics over time. Additionally Mean(SE) plot over time will be generated for the total score and a bar chart will be generated to graphically present the contribution of the subitems to the total score over time (see section 14.2.5. for calculation methods).
- The general health of the child was evaluated by completing a Visual Analogue Scale (VAS). VAS will be described using descriptive statistics (see Section 5.4.1 Summary statistics for details) of actual values over time. Additionally, Mean ( $\pm$ SE) plot will be used to present VAS graphically.
- Incidence of medical visit (at least one visit to doctor, hospital or emergency room as well as separately for each type of medical visit) will be tabulated.

#### 7.4 Subgroups Analysis

Subgroups analysis will be performed on the mITT population for the following subgroups:

- Age category: <6 months, 6 - <12 months and  $\geq$ 12 months
- Subjects with inadequate oral feeding and inadequate oxygen saturation at baseline vs other
- Co-infected subjects vs RSV only subjects

The analyses listed below will be performed on the subgroups mentioned above:

- Time to BQL based on the plaque assay summarized using Kaplan Meier estimates
- GSS, summarized using descriptive statistics of the actual values and the change from baseline over time
- Time to clinical response, summarized using Kaplan Meier estimates
- Time between first study drug administration and discharge, summarized using descriptives statistics and Kaplan Meier estimates

Subgroups analyses on subjects with inadequate feeding and inadequate oxygen saturation at baseline and co-infected subjects will be performed if at least 15% of the subjects have inadequate feeding and inadequate oxygen saturation at baseline, and are co-infected; respectively.

## 8 SAFETY

### 8.1 Adverse Events

#### 8.1.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. All AEs will be reported from the time a signed and dated ICF is obtained until completion of the subject's last visit.

A treatment emergent adverse event (TEAE) is defined as any adverse event starting or worsening in severity (for pre-existing conditions) from the start of study drug administration, until completion of the subject's last visit.

All tables will only present TEAE. Pre-treatment AEs will only be listed.

#### 8.1.2 Coding

All adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the time of database lock. The actual version used will be mentioned on AE outputs.

#### 8.1.3 Handling of missing AE information

Generally speaking a conservative approach is used to determine if an AE is treatment emergent in case of missing/partial onset date/time. (see section 14.3.1 for more details)

No imputation will be done of missing/partial date(time) fields. The dates and times will be presented in the listings as captured in the eCRF.

#### 8.1.4 Drug relatedness

Following ICH-E3, the drug relatedness as assessed by investigator will be dichotomized as follows:

- Drug related: at least possibly drug related, or with a missing drug relatedness
- Not drug related: less than possibly drug related.

#### 8.1.5 Calculation of Incidences of AEs

Incidence will be calculated on a subject level as the number (and percentage) of subjects for which the AE (preferred term or system organ class) was at least 1 time reported (within a treatment group) against the total number of subjects (within a treatment group). For the adverse event summary table (see Section 8.1.7) and the general TEAE table (All TEAE by SOC and PT) a separate count representing the number of events will be reported (without percentage).

### 8.1.6 Worst case reporting

When cross tabulating AE preferred terms versus an AE attribute (e.g., severity), the worst-case is always applied. I.e., when a subject has two times the same AE preferred term, then the subject is reported only once: only with the worst severity. A missing severity will not be imputed.

### 8.1.7 Analysis

A general summary table reporting the number and percentage of subjects, and the number of events will be provided. The following categories will be included in the summary table:

- Subjects with at least one TEAE
- Subjects with at least one serious TEAE
- Subjects with at least one severe TEAE
- Subjects with at least one TEAE leading to death
- Subjects with at least one TEAE for which the study drug was interrupted
- Subjects with at least one TEAE for which the study drug was withdrawn
- Subjects with at least one TEAE that was considered treatment-related
- Subjects with at least one serious TEAE that was considered treatment-related
- Subjects with at least one TEAE that was considered related to study procedure

A treatment-emergent analysis of AEs will be done. Frequency of subjects presenting with AEs, non-serious AEs, AEs leading to study drug withdrawal, AEs by maximum severity, related AEs by study drug relationship, AEs related to study procedures and SAEs will be tabulated for each treatment group by system organ class and preferred term.

The tables by system organ class and preferred term are sorted by decreasing frequency of SOC and PT (overall). If more than one SOC or PT have the same frequency, then the corresponding SOC and PT are sorted alphabetically.

A detailed list of Tables and Listings can be found in section 16.4 and section 18.3, respectively.

### 8.1.8 Subgroup analysis

The frequency of subjects with TEAEs will be provided by system organ class and preferred term for the subgroups defined in Section 7.4. These summaries will be sorted alphabetically by SOC and PT.

## 8.2 Laboratory Evaluations

### 8.2.1 Available data

The following tests will be included in the clinical laboratory analysis:

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- Clinical biochemistry: alanine aminotransferase, aspartate aminotransferase, creatinine, sodium, potassium, chloride, C-reactive protein,  $\gamma$ -glutamyl-transferase, blood urea nitrogen
- Hematology: hemoglobin, hematocrit, red blood cell count and indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential (lymphocytes, neutrophils, monocytes, basophils and eosinophils)

### 8.2.2 Laboratory units

The statistical analysis will only present results in Standard International (SI) units.

### 8.2.3 Abnormalities

All values will be compared to their matching normal ranges. The classification available in the standard data tabulation method (SDTM) dataset will not be used for the statistical analysis. The classification will be re-calculated in the analysis data model (ADaM) dataset by using the values and normal ranges in SI units. (See Section 14.3.2.2 for more details on abnormality classification).

### 8.2.4 Worst-case abnormality

The worst-case abnormality is derived for each parameter separately.

All non-missing post-baseline values (including unscheduled measurements and follow-up measurements) will be used to derive the worst-case. (see Section 14.3.2.3 for more details on worst-case abnormality classification).

### 8.2.5 Analysis

For laboratory parameters, descriptive statistics will be computed on the actual values and the change from baseline to Day 14 for each parameter according to general rules (see Section 5.4.1). In addition, all laboratory values will be categorized according to their normal ranges as abnormal low, normal or abnormal high. A shift table of worst post-baseline category versus baseline category will be created.

A detailed list of Tables and Listings can be found in section 16.5 and section 18.5, respectively.

## 8.3 Physical Examination

Abnormal findings in physical examinations (including heart auscultation, examination of abdomen, skin and ear/nose/throat) will be listed (see Section 16.4).

## 8.4 Vital Signs

The available parameters are: heart rate and weight. The actual values, change from baseline and percent change from baseline will be summarized over time using descriptive statistics (see Section 5.4.1). Heart rate will also be presented graphically in mean  $\pm$  SE Plot (excluding the in-hospital post-treatment timepoints).

A detailed list of tables, listings and figures can be found in Section 16.6, Section 18.6 and Section 17.5, respectively.

## 9 ANALYSIS OF PHARMACOKINETICS

See section 7.2.2.3 for details

## 10 ANALYSIS OF PHARMACODYNAMICS

Individual subject serum biomarker concentrations (KL-6) and collection times will be listed.

Biomarker results will be summarized as continuous variables by treatment and time point. Changes from baseline and percent changes from baseline will also be summarized (see Section 5.4.1 for more details) These summary statistics will also include the number and percentage of subjects with serum KL-6 levels that are below the lower limit of quantification (LLOQ) by treatment and time point. For the summary statistics, samples that are below the lower limit of quantification (LLOQ) will be assigned to the value of the LLOQ level. Biomarker results (actual values and change from baseline) will also be presented graphically in mean (arithmetic)  $\pm$  SE plots. In the listing the imputed values will be flagged and the LLOQ level will be reported in a footnote. The analysis will be performed on both mITT and RSV infected population

A detailed list of Tables and Listings can be found in section 16.7 and section 18.7, respectively.

## 11 IMMUNOGENICITY ANALYSIS

Immunogenicity will be assessed through summary tables and figures, and listing of individual results by subject.

A detailed list of tables, listings and figures can be found in Section 16.8, Section 18.9 and Section 17.7, respectively.

### 11.1 Available data

#### 11.1.1 ADA

Immunogenicity of ALX-0171 was monitored in all clinical studies using MSD-based homogeneous bridging ADA assays via a tiered approach. In a first step, samples are evaluated in a screening assay and are scored possibly ADA positive based on the screening

cut-point (SCP), allowing a 5% false positivity rate. Positively screened samples are subsequently analyzed in a confirmation assay, which is a drug displacement assay to confirm the specificity of the ADA screening result. All positively confirmed samples are subsequently analyzed in an end-point titration assay to determine the antibody titer. The  $\log_{10}(\text{titer})$  will be reported. The titer represents the last dilution factor of the sample's titration series still scoring positive in the ADA assay. Samples scoring negative in the ADA assay are not titrated and the respective  $\log_{10}(\text{titer})$  is reported as  $<\log_{10}(\text{Minimal required dilution [MRD]})$  with  $\text{MRD}=24$ , i.e.  $\log_{10}(\text{titer}) < 1.38$ . The latter negative samples are not included in descriptive statistics on titers.

For each subject, immunogenicity results will be categorised based on the presence of pre-existing antibodies (pre-Ab) and the presence of treatment-emergent (TE) ADA, as shown below. Classification is performed by the Bioanalytical laboratory (Ablynx GLP-Pharma) performing the ADA sample analysis and they report both  $\log_{10}(\text{titer})$  and subject classification.

Subjects will be classified based on the pre-Ab and TE ADA status (subject classifications):

1. Pre-Ab NEG – TE ADA NEG
2. Pre-Ab NEG – TE ADA POS
3. Pre-Ab POS – TE ADA NEG
4. Pre-Ab POS – TE ADA POS
5. Pre-Ab POS – TE ADA EQ
6. TE ADA inconclusive: Pre-Ab NEG – Post-dose missing
7. TE ADA inconclusive: Pre-Ab POS – Post-dose missing
8. TE ADA inconclusive: Pre-dose missing – Post-dose NEG
9. TE ADA inconclusive: Pre-dose missing – Post-dose POS

Note: Subject classification 'Inconclusive TE ADA' (that is generally used in case drug tolerance is exceeded) is not included here since drug washout samples are available for ADA testing.

Below subject categories are only to be used in the tables and figures on incidence and subgroup analysis (for all other figures and tables subject classifications are used as described above).

Possible subject categories:

1. Pre-Ab NEG – TE ADA NEG
2. Pre-Ab NEG – TE ADA POS
3. Pre-Ab POS – TE ADA NEG
4. Pre-Ab POS – TE ADA POS
5. Pre-Ab POS – TE ADA EQ
6. TE ADA inconclusive: Pre-Ab NEG – Post-dose missing
7. TE ADA inconclusive: Pre-Ab POS – Post-dose missing
8. TE ADA inconclusive: Pre-dose missing – Post-dose NEG
9. TE ADA inconclusive: Pre-dose missing – Post-dose POS



10. Total Pre-Ab NEG (“Pre-Ab NEG – TE ADA NEG”, “Pre-Ab NEG – TE ADA POS” and “Pre-Ab NEG – Post-dose missing”)
11. Total Pre-Ab POS (“Pre-Ab POS – TE ADA NEG”, Pre-Ab POS – TE ADA POS”, “Pre-Ab POS – TE ADA EQ” and Pre-Ab POS – Post-dose missing”)
12. Total TE ADA NEG (“Pre-Ab NEG – TE ADA NEG” and “Pre-Ab POS – TE ADA NEG”)
13. Total TE ADA POS (“Pre-Ab NEG – TE ADA POS” and “Pre-Ab POS – TE ADA POS”)
14. TE ADA POS within Pre-Ab NEG
15. TE ADA POS within Pre-Ab POS

### 11.1.2 NAb

All samples screened and confirmed positive in the ADA assay will be analyzed in the NAb assay. NAb assay results will be reported as values (ratio is optical density (OD) value over negative control (NC)). No titration will be performed.

Subjects will be classified based on their pre-dose status (i.e. baseline visit) and status on treatment as shown below. Subject classification based on NAb is performed by the external provider (Eurofins, UK) performing NAb sample analysis and they report both ratio (for all analysed samples) and NAb subject classification:

1. Pre-dose Neg – Neg on treatment
2. Pre-dose Neg – Pos on treatment
3. Pre-dose Pos – Neg on treatment
4. Pre-dose Pos – Pos on treatment
5. Pre-dose Neg – Post-dose missing
6. Pre-dose Pos – Post-dose missing
7. Pre-dose missing – Neg on treatment
8. Pre-dose missing – Pos on treatment

Subjects with no positive ADA samples, will not be analyzed in the NAb assay and will be classified as Pre-dose Neg - Neg on treatment. In listings, samples not evaluated in the NAb assay will be indicated as not analyzed (NA).

Below subject categories are only to be used in the tables and figures on incidence and subgroup analysis (for all other figures and tables subject classifications are used as described above).

Possible subject categories:

1. Pre-dose Neg – Neg on treatment
2. Pre-dose Neg – Pos on treatment
3. Pre-dose Pos – Neg on treatment
4. Pre-dose Pos – Pos on treatment
5. Pre-dose Neg – Post-dose missing
6. Pre-dose Pos – Post-dose missing
7. Pre-dose missing– Neg on treatment
8. Pre-dose missing – Pos on treatment
9. Total Pre-dose negative (“Pre-dose Neg – Neg on treatment”, “Pre-dose Neg – Pos on treatment” and “Pre-dose Neg – Post-dose missing”)



10. Total Pre-dose positive (“Pre-dose Pos – Neg on treatment”, “Pre-dose Pos – Pos on treatment” and “Pre-dose Pos – Post-dose missing”)
11. Total Neg on treatment (“Pre-dose Neg – Neg on treatment’, “Pre-dose Pos – Neg on treatment”, “Pre-dose missing-Neg on treatment”)
12. Total Pos on treatment (“Pre-dose Neg – Pos on treatment’, “Pre-dose Pos – Pos on treatment”, “Pre-dose missing-Pos on treatment”)
13. Pos on treatment within Pre-dose Neg
14. Pos on treatment within Pre-dose Pos

## 11.2 Analysis

Immunogenicity analyses will be summarized by treatment group (placebo, ALX0-171 3.0 mg/kg, ALX-0171 6.0 mg/kg and ALX-0171 9.0 mg/kg) and overall (ALX-0171 TOTAL).

The incidence of TE ADA and pre-Ab status based on ADA assay results will be tabulated, as well as the incidence of TE ADA and pre-Ab status based on NAb assay results.

All Immunogenicity data will be listed

### 11.2.1 Subgroup analyses

Analysis of incidence based on ADA results are planned for the following subgroups:

- Hypersensitivity reaction, based on the SMQs ‘Hypersensitivity’ (Narrow), ‘Anaphylactic reaction’ (Narrow) and ‘Angioedema’ (Narrow), with categories
  - No hypersensitivity reaction
  - At least 1 hypersensitivity reaction

### 11.2.2 Correlation of immunogenicity with PK, efficacy and safety

The drug concentrations with actual sampling times within time windows per study protocol, will be summarized over time for the subjects with extensive PK sampling, by a subset of ADA (Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) and NAb (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment) subject categories. Drug concentrations will also be presented graphically in mean  $\pm$  SE plots. Scatterplots displaying drug concentrations and time will be generated by ADA and NAb subject categories pre-specified above, for each treatment group.

The mean change from baseline (to Day 2, 5 hours post dose) in Global Severity Score (GSS) will be summarized by a subset of ADA (Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) and NAb (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment) subject categories, for each treatment group. Scatterplot displaying change from baseline in GSS score (to Day 2,5 hours post dose) will be generated by ADA and NAb subject categories pre-specified above, for each treatment group.

The viral load (time to BQL – plaque assay) will be summarized using Kaplan Meier estimates, by a subset of ADA (Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) and NAb (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment) subject categories, for each treatment group. Viral load (time to BQL – plaque assay) will also be presented graphically by Kaplan Meier survival curves for each ADA and NAb subject categories pre-specified above, by treatment group.

## 12 INTERIM ANALYSES

No interim analysis is foreseen for this study.

After the sequential part of the study (see Figure 1: Overview of study design) an evaluation of the relationship between the different ALX-0171 dose levels and the corresponding plasma concentration levels was performed by a separate unblinded team at the CRO. This team remained independent from the main study team to ensure blinding of the study and only provided a general recommendation to the sponsor. Please refer to Appendix B: Concentration assessment plan for more detailed information.

## 13 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Additional analysis on the primary endpoint was added using a Cox proportional hazards regression model with time to BQL as dependent variable, and treatment group, viral load at baseline and co-infected subject group as independent variables. These changes will not lead to an amendment of the clinical trial protocol

Following endpoints were added:

- Time between first study drug administration and discharge
- Duration of severe disease
- Duration of feeding support
- Subgroup analyses have been added for selected efficacy and safety endpoints

## 14 CONVENTIONS

### 14.1 General data handling rules

#### 14.1.1 Analysis time points

All by-time-point summaries will be based on the visit indicated on the subject's CRF.

Trial window = (time window, delimited by ICF and trial termination)

### 14.1.2 Relative number of days

The relative day (DY) is calculated as follows:

- = Assessment date – reference date + 1 day, when the assessment date is on or after the reference date
- = Assessment date – reference date, when the assessment date is before the reference date
- = Missing, when the assessment date is missing or incomplete.

The reference date in the study is **date of first dose**, which by definition has DY=1. There is no DY=0.

### 14.1.3 Handling of unscheduled assessments

Generally, only the original scheduled assessments will be used for the analysis tables and unscheduled assessments will only be shown in listings. However, unscheduled assessments will be used for analysis tables in the following cases

- Use as baseline (see section 5.3.1)
- Worst-case determination over a period of time.
- Time to calculation e.g. Nasal mid-turbinate swab collected at unscheduled visits will be used to determine the time-to-BQL and time to undetectability.
- AUC calculation
- LOCF imputation of missing individual GSS items (see section 14.2.2)

### 14.1.4 Prior and Concomitant medication: Handling of missing/partial date

In case of missing or partial start or stop dates, no imputations will be performed, the therapy will be classified as prior or concomitant, as reported in the CRF.

### 14.1.5 Number of days between symptom onset and first dose of study drug: Handling of missing time part

Number of days between symptom onset and first dose of study drug is defined as the time between start of the symptom(s) (RSV disease characteristics) and first dose.

If needed time for start of the symptoms will be imputed with 00:00.

## 14.2 Efficacy

### 14.2.1 Viral load

#### 14.2.1.1 Area under the curve (AUC)

The area under the curve (from first study drug administration to time t) is the total viral load concentration over time. The total area is a plot of viral load (Y-axis) versus time (X-axis). The X-axis starts at timepoint t=0 (first study drug administration) and ends at last measurement (timepoint=t). The Y-axis represents the actual concentration at timepoint t. The AUC will mathematically correspond to the definite integral of the function (concentration curve). In

practice, the actual concentration is measured at certain discrete points in time and the trapezoidal rule is used to estimate AUC:

- $AUC(0) = 0$  at baseline  $t=0$ .
- $AUC(t) = AUC(t-1) + 0.5 * (Value(t-1)+Value(t)) * (time(t)-time(t-1))$  = cumulative AUC up to time  $t$ .

The actual times will be used to derive the AUC.

Rules on how to deal with missing values when deriving the AUC:

- If the baseline value is missing, then all AUCs will be set to missing.
- If single intermediate values (not the baseline nor the last value, and not more than 3 (in total, not consecutive)) are missing, then the missing value will be replaced by linear interpolation of the two adjacent values. Note: this is done automatically when applying the trapezoidal summation rule.
- If multiple ( $>1$ ) adjacent values are missing or more than 3 values are missing, then the AUC will also be set to missing.
- Unscheduled assessments will be considered for AUC calculation but will not be considered when defining the number of missing values.

#### 14.2.1.2 Time weighted average change from baseline to time $t$

- Time weighted average change from baseline to time  $t$  will be calculated as:

$$[AUC(t) - (\text{baseline value} * t)] / t.$$

For subjects who only have data up to time  $x (< t)$ , the time weighted average change from baseline to time  $t$  is defined as:  $[AUC(x) - \text{baseline value} * x] / x$ .

#### 14.2.2 Global Severity Score (GSS)

GSS will be calculated by summing the scores of 7 individual items (see below). Maximum score is 20 with higher score indicating a more severe disease.

For the computation of the baseline GSS, the baseline value of each individual item is first identified (some may be from Day 1 pre-dose and others from screening). The individual item baseline values are then summed to obtain the baseline GSS.

Apnea, hospital stay, oxygen supplementation, and ventilation will be considered respectively to have occurred at the considered visit and time point if they are reported over a period that covers at least partly the time interval defined for this visit using following definitions for time intervals:

- for baseline : from hospital admission to first study drug administration,
- for post-baseline visits and timepoints during treatment as:
  - starting from the minimum between:
    - the end of the previous interval,
    - the earliest date and time a GSS component was assessed at the considered visit and timepoint, and
    - 1 minute before the latest date and time a GSS component was assessed at the considered visit and timepoint

- - ending at the latest date and time a GSS component was assessed at the considered visit and timepoint.
- for all ‘Post-Treatment Day n’ visits:
  - the “MORNING” timepoint will be assigned to time interval 00:00 – 11:59 of the date of the considered visit and timepoint
  - the “EVENING” timepoint will be assigned to time interval 12:00 – 23:59 of the date of the considered visit and t timepoint
- The “Follow-UP” visit and unscheduled post-treatment visits will be assigned to time interval 00:00 – 23:59 of the date of the considered visit and timepoint. This implies that there will be a gap between the follow-Up visit and the previous timepoint, and that every hospitalization / apnea / ventilation / oxygen supplementation recorded that would be entirely within that gap will not be taken into account into GSS score computed at any timepoint.

This implies that a recorded item (hospitalization / apnea / ventilation / oxygen supplementation) may contribute to more than one time interval for the GSS calculation.

Item	Number of Points	Description
Feeding	0	Adequate oral feeding
	1	No adequate oral feeding, occasional breaks during feeding
	2	No adequate oral feeding, frequent breaks during feeding
	3	No adequate oral feeding, unable to feed, or on feeding support
Medical interventions	0	Not hospitalized
	1	Hospitalization without O <sub>2</sub> supplementation
	2	Conventional oxygen supplementation
	3	Non-invasive respiratory support or invasive ventilation
Respiratory distress	0	RDAI = 0
	1	RDAI ≥ 1 to < 6
	2	RDAI ≥ 6 to ≤ 11
	3	RDAI > 11
Respiratory rate	0	<2 months: ≤50 bpm; 2-<6 months: ≤45 bpm; 6-<12 months: ≤40 bpm; 12-24 months: ≤35 bpm
	1	<2 months: >50 to ≤60 bpm; 2-<6 months: >45 to ≤55 bpm; 6-<12 months: >40 to ≤50 bpm; 12-24 months: >35 to ≤45 bpm
	2	<2 months: >60 to ≤70 bpm; 2-<6 months: >55 ≤ 60; 6-<12 months: >50 to ≤55 bpm; 12-24 months: >45 to ≤50 bpm
	3	<2 months: >70 bpm; 2-<6 months: >60 bpm; 6-<12 months: >55 bpm; 12-24 months: >50 bpm
Apnea	0	No apnea episode
	3	Apnea episode
General appearance <sup>a</sup>	0	Active, playing/ content/ interactive and happy
	1	Less active/ mildly irritable/ less interactive or responsive
	2	Less active/ moderately irritable/ less interactive or responsive
	3	Not active/ Severely irritable/ Not interactive or not responsive

Note: In case worst item is less active and/or less interactive: if both are present: 2 points; if only one of both is present and the highest: 1 point

Body Temperature	0	<37,0°C: (measured axillary); <37,5°C (measured by other method)
	1	≥37,0°C but <38°C (measured axillary); ≥37,5°C but <38,5°C (measured by other method)
	2	≥38°C (measured axillary); ≥38,5°C (measured by other method)

<sup>a</sup> Assessed through activity, irritation and interest in environment (worst of the three items will be used for attributing the points)

Following imputation will be done for missing data :

- For General appearance, scoring will be done only on completed items and only the worst item is used for scoring.
- If more than two individual items (i.e., feeding, medical intervention, RDAI, respiratory rate, general appearance and body temperature) are missing at a given timepoint GSS will be set to missing for this timepoint
- If maximum 2 individual items are missing at a timepoint, missing items will be imputed using LOCF approach and the GSS will be calculated after imputation of the individual item(s).
- 

Imputed items will be flagged in the listings.

### 14.2.3 Respiratory Distress Assessment Instrument (RDAI)

RDAI is a 17-point score based on wheezing and retraction (see below).

Variable	Number of Points					Maximum Points
	0	1	2	3	4	
<b>Wheezing</b>						
Expiration	None	End	1/2 period	3/4 period	All	4
Inspiration	None	Part	All	NA	NA	2
Location	None	Segmental ≤ 2 of 4 lung fields	Diffuse ≥ 3 of 4 lung fields	NA	NA	2
<b>Retractions</b>						
Supraclavicular	None	Mild	Moderate	Marked	NA	3
Intercostal	None	Mild	Moderate	Marked	NA	3
Subcostal	None	Mild	Moderate	Marked	NA	3

NA = not applicable

The RDAI score is the sum of the row scores, with total range 0 to 17; higher scores indicate more severe disease.

No imputation of missing data will be performed

#### 14.2.4 Respiratory Assessment Change Score (RACS)

The RACS score is the sum of the change from baseline in the RDAI score and a standardised score for the change from baseline in respiratory rate. The change in respiratory rate is assigned 1 point per each 10% change in the respiratory rate.

A decrease in the sum of the RDAI and the respiratory rate during the study period is recorded as a negative RACS, meaning an improvement.

If change in respiratory rate is missing, missing value will be imputed using an LOCF imputation. Imputed values will be flagged in the listings.

#### 14.2.5 Respiratory symptoms score

Based on the information collected in the diary (regarding cough, trouble breathing and wheezing), a respiratory symptoms score will be calculated. The score will range from 0 to 5. A subitem score for each of the respiratory symptoms (cough, trouble breathing and wheezing) will be calculated using the following scoring:

Severity	Score
No	0
Very mild	1
Mild	2
Moderate	3
Severe	4
Very severe	5

The respiratory symptoms score will be calculated by taking the sum over all non-missing subitems and dividing by the number of non-missing items. In case more than 1 subitem is missing the total score will also be set to missing.

#### 14.2.6 Duration of supplemental oxygen therapy

This is based on concomitant medication records.

For Baseline assessment a subject is considered being on oxygen supplementation at baseline if oxygen was received between hospital admission and the first dose of study medication. For this derivation, both prior and concomitant medications are considered

Total duration will be calculated as the total number of hours (taking into account the sum of the actual time windows the concomitant medication was received) using concomitant treatment coded as "Oxygen" from admission until trial termination and from first dose until trial termination. Missing information on concomitant medication records will be imputed in the following way

- If start time is missing: impute with 0:00 .

- If end time is missing: impute with 23:59.
- If start day/month is missing: impute with first day (01) / month (Jan) if this falls within trial window, otherwise impute with day/month of first contact in the trial.
- If end day/month is missing: impute with last day (31) / month (Dec) if this falls within trial window, otherwise impute with day/month of trial termination.

In case of overlapping records, the duration will be calculated only once for the overlapping part of the records.

#### 14.2.7 Duration of feeding support

This is based on concomitant medication records.

For Baseline assessment a subject is considered being on feeding support at baseline if support was received between hospital admission and the first dose of study medication. For this derivation, both prior and concomitant medications are considered

Following coded terms will be considered for feeding support provided the route of administration is intravenous or nasogastric.

AMINO ACIDS NOS  
AMINOVEN  
CALCIUM GLUCONATE  
DEXTROSE AND SODIUM CHLORIDE INJECTION  
DEXTROSE IN LACTATED RINGER'S  
ELECTROLYTES NOS  
ELECTROLYTES NOS W/GLUCOSE  
GLUC5% W/RINGER BAXTER  
GLUCOSE  
GLUKOSALINA /06282701/  
INFANT FORMULAS  
ISOLYTE /06504901/  
ISOLYTE P DEXTROSA  
JONOSTERIL /01263001/  
MAGNESIUM SULFATE  
MATERNA /02266601/  
OSMOTAN  
POTASSIUM CHLORIDE  
PROTEIN HYDROLYSATE  
RICE /08368701/  
RINDEX /07339201/  
RINGER-LACTATE



SODIUM CHLORIDE  
SODIUM GLYCEROPHOSPHATE

Total duration will be calculated as the total number of hours (taking into account the sum of the actual time windows the concomitant medication was received) using concomitant treatment from the above list from admission until trial termination and from first dose until trial termination. Missing information on concomitant medication records will be imputed in the following way

- If start time is missing: impute with 0:00 .
- If end time is missing: impute with 23:59.
- If start day/month is missing: impute with first day (01) / month (Jan) if this falls within trial window, otherwise impute with day/month of first contact in the trial.
- If end day/month is missing: impute with last day (31) / month (Dec) if this falls within trial window, otherwise impute with day/month of trial termination.

In case of overlapping records, the duration will be calculated only once for the overlapping part of the records.

**14.2.8 Duration and type of ventilation**

This is based on CRF procedure information (PR domain). Total duration of invasive and non-invasive ventilation (in hours) will be calculated as the sum of all durations from first dose until trial termination per category and subject. Missing information on individual records will be imputed in the following way

- If start time is missing: impute with 0:00 .
- If end time is missing: impute with 23:59.
- If start day/month is missing: impute with first day (01) / month (Jan) if this falls within trial window, otherwise impute with day/month of first contact in the trial.
- If end day/month is missing: impute with last day (31) / month (Dec) if this falls within trial window, otherwise impute with day/month of trial termination.

In case of overlapping records, the duration will be calculated only once for the overlapping part of the records. .

**14.2.9 Duration of hospital/ICU stay:**

Defined as the time between hospital admission and discharge (in days)

- If start time is missing: impute with 0:00.
- In case end time is missing: impute with 18:00 .
- If start day/month is missing: impute with first day (01) / month (Jan) if this falls within trial window, otherwise impute with day/month of first contact in the trial.
- If end day/month is missing: impute with last day (31) / month (Dec) if this falls within trial window, otherwise impute with day/month of trial termination.

In case the subject is still hospitalized at the end of the trial, the trial termination date will be used.

#### **14.2.10 Duration of hospital stay for RSV**

The time between hospital admission and discharge (in days), similar to regular hospital stay but excluding prolongation due to SAE other than RSV worsening. SAE considered as RSV worsening are selected on SOC (“Respiratory, thoracic and mediastinal disorders” or “infections and infestations”) and PT (for infections and infestations only) by:

- Including any from: ‘bronchiolitis’, ‘pneumonia’, ‘bronchitis’, ‘RSV’
- Excluding ‘bacterial’

Imputation rules follow the rules for duration of hospital stay. Subject with a prolongation due to SAE other than RSV worsening will be censored at the SAE onset date.

#### **14.2.11 Time between first study drug administration and discharge**

Defined as the time between first study drug administration and discharge (in days).

Imputation rules follow the rules for duration of hospital stay.

In case the subject is still hospitalized at the end of the trial, the trial termination date will be used.

#### **14.2.12 Time to child’s condition as before RSV onset**

Time to child’s condition as before RSV onset (in days) is defined as the time between first study drug administration and the first time the subject reaches the condition as before RSV onset as documented by the general health questionnaire. In case the subject does not reach the condition as before RSV, the time is censored at the last day with caregiver assessment equal to ‘No’.

### **14.3 Safety**

#### **14.3.1 Adverse Events**

##### **14.3.1.1 Handling of missing/partial date/time**

In case the adverse event (AE) start date(time) is incomplete, a conservative approach will be taken based on the available parts of the AE start date(time).

If the AE start time is missing and the AE start date is equal to or after the first date of study drug administration, then the AE is considered treatment emergent. If the day on which the AE started is missing and the month & year are the same or after the month & year of the start

of study drug administration or if the day and month on which the AE started are missing and the year is the same or after the year of the start of study drug administration, then the AE is considered treatment emergent (unless the AE end date is before the first study drug administration).

#### **14.3.1.2 Calculation of derived variables**

Following derived variables will be calculated:

AE duration

- = AE stop date – AE start date + 1 day (when both dates are completely known)
- = trial termination date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as “>x days” in the listing rather than “x days”
- = missing (when the AE start date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date).

#### **14.3.2 Laboratory Evaluations**

##### **14.3.2.1 Handling of missing data: Differential blood cell counts**

In case of missing differential blood cell count, if either the absolute count or % is missing, the other one will be re-calculated on the available data if possible. Both values will be reported.

##### **14.3.2.2 Abnormal values**

Values will be scored as abnormally low (L), normal (N) or abnormally high (H). A value is classified as abnormally low when the value < lower limit of the normal range. A value is classified as abnormally high when the value > upper limit of the normal range. Laboratory parameters without quantitative values reported but indicated as NEGATIVE will be categorized as normal and values indicated as POSITIVE will be categorized as abnormal high. Values below the upper limit but without lower limit provided will be categorized as normal. Other tests without normal ranges will not be scored. An original value like “<X” where X equals the lower limit of the normal range will be classified as abnormally low (L). An original value like “>X” where X equals the upper limit of the normal range will be classified as abnormally high (H).

##### **14.3.2.3 Worst Case abnormalities**

Following categories will be used in the analysis

- H = abnormally high: at least one post-dose measurement is above the normal range, and there are no values below the normal range.
- L = abnormally low: at least one post-dose measurement is below the normal range, and there are no values above the normal range.

- H+L = abnormally high and low: at least one post-dose measurement is above the normal range, and at least one other post-dose measurement is below the normal range.
- N = normal: all post-dose measurements are within normal limits

#### 14.3.2.4 Handling of values below (or above) a threshold for descriptive statistics

For general safety labs values below (above) the detection limit will be imputed by the value of the detection limit itself, unless indicated otherwise. For virology results, values below the lower limit of quantification will be imputed by half of the value of the lower limit of quantification itself. For KL-6, values below the lower limit of quantification will be imputed by the value of the lower limit of quantification.

Listings will always present the original value. Example: if the database contains values like “<0.04”, then for the descriptive statistics the value of the detection limit (0.04) shall be used. A value like “>1000” will be imputed by “1000”.

## 15 REFERENCE LIST

1. Ralston, S.L., et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*, 2014. 134(5): p. e1474-502.
2. National Institute for Health and Care Excellence (NICE), Guideline in development - Bronchiolitis: Diagnosis and Management of Bronchiolitis in Children, 2015: London.
3. Meissner, H.C. Viral Bronchiolitis in Children. *The New England journal of medicine*, 2016. 374(1): p. 62-72.
4. Mazur, N.I., et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *The Lancet. Respiratory medicine*, 2015. 3(11): p. 888-900.

## 16 INDEX OF TABLES

Tables and figures which will be part of the topline results are flagged with “(T)” in the titles.

### 16.1 General

#### Table 14.1.1.1: Subject disposition: Tabulation by analysis population

Tabulation of the number of subjects in each of the analysis populations.

Population: all screened population.

#### Table 14.1.1.2: Subject disposition: Tabulation by country and site

Tabulation of the number of subjects per country and site.

Population: ITT.

**Table 14.1.1.3: Subject disposition: First and last contact in the trial**

List the following 3 dates:

- Date of the first signature on study ICF or RSV test ICF
- Last visit date (all visits; including unscheduled visits)
- Last date of contact in the study with any subject.

Population: all screened population.

**Table 14.1.1.4: Screening failures and Treatment and Trial termination: Tabulation (T)**

Tabulation of:

number of screened, randomized and treated subjects and number of screening failures, together with primary reason for failure

trial and treatment completion/discontinuations and the reasons for discontinuation.

Population: all screened population.

**Table 14.1.1.5: Major Protocol deviations: Tabulation**

Tabulation of the protocol deviations per class.

Population: mITT.

**Table 14.1.1.6: Major Protocol deviations leading to exclusion from the per protocol population: Tabulation**

Tabulation of the protocol deviations leading to exclusion of the PP population per class.

Population: RSV infected.

**Table 14.1.2.1: Demographic data: Tabulation and descriptive statistics (T)**

Continuous parameters: descriptive statistics.

Categorical parameters: frequency tabulation.

Part 1: Modified intent-to-treat population.

Part 2: RSV infected population

Part 3: Per protocol population

**Table 14.1.2.2: Baseline disease characteristics: Tabulation and descriptive statistics (T)**

Continuous parameters: descriptive statistics.

Categorical parameters: frequency tabulation.

Part 1: Modified intent-to-treat population.

Part 2: RSV infected population

Part 3: Per protocol population

**Table 14.1.2.3: Baseline disease characteristics: Viral screening tests (T)**

Frequency tabulation per group of the results of the viral screening tests (refer to 19.4 for complete list)

Part 1: Modified intent-to-treat population.

Part 2: RSV infected population

Part 3: Per protocol population

**Table 14.1.2.4: Medical history: Tabulation by category**

Tabulation of medical history by category. Table entries are sorted alphabetically by category.

Population: mITT population.

**Table 14.1.2.5: Prior therapies by ATC 4 class and generic term**

Tabulation of the generic terms and ATC level 4 code of previous therapies.

Population: safety population.

**Table 14.1.2.6: Concomitant therapies by ATC 4 class and generic term**

Tabulation of the generic terms and ATC level 4 code of concomitant therapies.

Population: safety population.

**Table 14.1.2.7: Exposure to study medication: administration per day**

Tabulation of number of subjects with administration per day/timepoint. Includes frequency tabulation on compliance parameters:

Population: safety population.

**Table 14.1.2.8: Exposure to study medication: Compliance**

Descriptive statistics on treatment compliance

Population: safety population.

## 16.2 Efficacy

**Table 14.2.1.1: Primary Endpoint: Time to below quantification limit of RSV viral load (plaque assay) (T)**

Kaplan-Meier analysis, including a two-sided Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test. Additionally the results of a Cox proportional hazards regression model with time to BQL as dependent variable, and treatment group, viral load at baseline and co-infected subject group as independent variables will be reported including Hazard ratio (95% CI) and p-value

Population: mITT population.

**Table 14.2.1.2: Sensitivity analysis - Time to below quantification limit of RSV viral load (plaque assay)-RSV Infected population (T)**

Kaplan-Meier analysis, including a two-sided Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test. Additionally the results of a Cox proportional hazards regression model with time to BQL as dependent variable, and treatment group, viral load at baseline and co-infected subject group as independent variables will be reported including Hazard ratio (95% CI) and p-value

Population: RSV infected population.

**Table 14.2.1.3: Sensitivity analysis - Time to below quantification limit of RSV viral load (plaque assay)-Per Protocol analysis (T)**

Kaplan-Meier analysis, including a two-sided Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test. Additionally the results of a Cox proportional hazards regression model with time to BQL as dependent variable, and treatment group, viral load at baseline and co-infected subject group as independent variables will be reported including Hazard ratio (95% CI) and p-value

Population: Per Protocol population.

**Table 14.2.1.4: Key Secondary endpoint - Global severity score – Change from baseline to Day 2, 5h mixed model. (T)**

Overall mixed model on the change from baseline to Day 2, 5 hours post dose with random factor subject and fixed effects baseline value, treatment group and timepoint including the treatment-by-timepoint interaction term. Contrast p-values for the individual pair-wise comparisons will be reported.

Population: mITT population.

**Table 14.2.1.5: Key Secondary endpoint - Global severity score – Change from baseline to Day 2, 5h mixed model - RSV infected population. (T)**

Overall mixed model on the change from baseline to Day 2, 5 hours post dose with random factor subject and fixed effects baseline value, treatment group and timepoint including the treatment-by-timepoint interaction term. Contrast p-values for the individual pair-wise comparisons will be reported.

Population: RSV infected population.

**Table 14.2.1.6: Key Secondary endpoint - Global severity score – Change from baseline to Day 2, 5h mixed model - Per Protocol Population. (T)**

Overall mixed model on the change from baseline to Day 2, 5 hours post dose with random factor subject and fixed effects baseline value, treatment group and timepoint including the treatment-by-timepoint interaction term. Contrast p-values for the individual pair-wise comparisons will be reported.

Population: PP population.

**Table 14.2.1.7: Global Severity score – Actual values and change from baseline per timepoint. (T)**

Descriptive statistics of GSS and individual subitems (actual values and change from baseline ) per timepoint.

Part 1 : Modified intent-to-treat population.

Part 2 : RSV infected population

**Table 14.2.2.1: Time to clinical response, Time to adequate oxygen saturation and time to adequate oral feeding (T)**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CI for both parameters separately and combined

Population: mITT population.



**Table 14.2.2.2: Duration of Severe disease**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CI  
Population: mITT population.

**Table 14.2.3.1: Viral load: Time to below quantification limit of RSV viral load (RT-qPCR assay)**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs  
Part 1 : Modified intent-to-treat population.  
Part 2 : RSV infected population

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Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs  
Part 1 : Modified intent-to-treat population.  
Part 2 : RSV infected population

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Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs  
Part 1 : Modified intent-to-treat population.  
Part 2 : RSV infected population

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Part 2 : RSV infected population

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Descriptive statistics of actual values and percent change from baseline of respiratory rate per timepoint

Population: mITT population.

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Population: mITT population

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Population: mITT population.

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Frequency tabulation reporting the number and percentages of subjects with clinical symptoms per timepoint. Include all categories (adequate feeding, feeding support)

Population: mITT population.

**Table 14.2.4.6: Evolution of clinical symptoms - Respiratory distress - Frequency tabulation of symptoms over time.**

Frequency tabulation reporting the number and percentages of subjects with clinical symptoms per timepoint. Include all Symptom categories (Wheezing (during inspiration/expiration), lung fields affected, crackles/crepitations, respiratory muscle retractions (supravascular, intercostal and subcostal)

Population: mITT population.

**Table 14.2.4.7: Evolution of clinical symptoms - Cough - Frequency tabulation of symptoms over time.**

Frequency tabulation reporting the number and percentages of subjects with clinical symptoms per timepoint. Include all Symptom categories (Daytime coughing, sleep disturbance)

Population: mITT population.

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Population: mITT population.

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Descriptive statistics of RDAI values (actual values and change from baseline) over time.

Population: mITT population.

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Descriptive statistics of actual RACS values over time.

Population: mITT population.

**Table 14.2.6.1: Hospitalisation – Length of hospital stay.**

Descriptive statistics of total length of hospital stay and Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs.

Population: mITT population.

**Table 14.2.6.2: Hospitalisation – Length of hospital stay for RSV.**

Descriptive statistics of total length of hospital stay and Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs.

Population: mITT population.

**Table 14.2.6.3: Hospitalisation – Time between first study drug administration and discharge.**

Descriptive statistics of time between first dose and discharge and Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs.

Population: mITT population.

**Table 14.2.6.4: Hospitalisation – Total time of reported oxygen supply.**

Descriptive statistics of total time of oxygen supply. Both time from admission to EOS as time from first dose to EOS will be reported

Population: mITT population.

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Descriptive statistics of total time of feeding support. Both time from admission to EOS as time from first dose to EOS will be reported

Population: mITT population.

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Population: mITT population.

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Cross tabulation of feeding support post-baseline versus baseline.

Population: mITT population.

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Population: mITT population.

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Population: mITT population.

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Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs  
Population: mITT population.

**Table 14.2.7.2: Parent/Caregiver assessment – Frequency tabulation over time.**

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Population: mITT population.

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Population: mITT population.

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Population: mITT population.

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Population: mITT population.

## 16.3 Subgroup analysis

**Table 14.2.8.1: Subgroup analysis: Time to below quantification limit of RSV viral load (plaque assay)**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs

Population: mITT population.

Part 1: By Age category

Part 2: By RSV Severity at baseline

Part 3: By Co-infection status

**Table 14.2.8.2: Subgroup analysis: Global Severity score – Actual values and change from baseline per timepoint.**

Descriptive statistics of GSS and individual subitems (actual values and change from baseline ) per timepoint.

Population: mITT population.

Part 1: By Age category

Part 2: By RSV Severity at baseline

Part 3: By Co-infection status

**Table 14.2.8.3: Subgroup analysis: Time to clinical response**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CI

Population: mITT population.

Part 1: By Age category

Part 2: By RSV Severity at baseline

Part 3: By Co-infection status

**Table 14.2.8.4: Subgroup analysis: Hospitalisation – Time between first study drug administration and discharge.**

Descriptive statistics of time between first dose and discharge and Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs.

Population: mITT population.

Part 1: By Age category

Part 2: By RSV Severity at baseline

Part 3: By Co-infection status

## 16.4 Safety: Adverse Events

**Table 14.3.1.1: Treatment-emergent adverse events: Summary table (T)**

Tabulation of the number and percentage of subjects and events for the following:

- Subjects with at least one treatment-emergent adverse event (TEAE)
- Subjects with at least one serious TEAE
- Subjects with at least one TEAE leading to death
- Subjects with at least one severe TEAE as classified by the investigator
- Subjects with at least one TEAE for which the study drug was interrupted

- Subjects with at least one TEAE for which the study drug or study was discontinued
- Subjects with at least one TEAE that was considered treatment-related
- Subjects with at least one serious TEAE that was considered treatment-related
- Subjects with at least one TEAE that was considered related to study procedure

Population: safety population.

**Table 14.3.1.2: Treatment-emergent adverse events: Tabulation of all adverse events (T)**

Tabulation of TEAE preferred terms per system organ class and preferred term.

Population: safety population.

**Table 14.3.1.3: Treatment-emergent adverse events: Tabulation of all adverse events by maximum severity**

Tabulation of TEAE preferred terms per system organ class by maximum severity.

Population: safety population.

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Tabulation of non-serious TEAE preferred terms per system organ class.

Population: safety population.

**Table 14.3.1.5: Treatment-emergent adverse events: Tabulation of serious adverse events (T)**

Tabulation of serious TEAE preferred terms per system organ class.

Population: safety population.

**Table 14.3.1.6: Treatment-emergent adverse events: Tabulation of all treatment-related events by relationship (T)**

Tabulation of TEAE preferred terms per system organ class. Selecting only the TEAEs that were treatment-related.

Population: safety population.

**Table 14.3.1.7: Treatment-emergent adverse events: Tabulation of the events for which the study medication was discontinued (T)**

Tabulation of TEAE preferred terms per system organ class. Selecting only the TEAEs for which the study treatment was permanently discontinued

Population: safety population.

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Tabulation of TEAE preferred terms per system organ class. Selecting only the TEAEs that were procedure related

Population: safety population.

**Table 14.3.1.9: Subgroup analysis: Treatment-emergent adverse events: Tabulation of all adverse events by subgroup**

Tabulation of TEAE preferred terms per system organ class and preferred term.

Population: safety population.

Part 1: By Age category

Part 2: By RSV Severity at baseline

Part 3: By Co-infection status at baseline

## 16.5 Safety: Laboratory

### **Table 14.3.2.1: Laboratory data: Descriptive statistics of the actual values and change from baseline per time point**

Descriptive statistics per lab test category (hematology, biochemistry), lab test and unit and time point. Table sorted first by treatment group, then by time point. Each lab test will begin on a new page.

Population: safety population.

### **Table 14.3.2.2: Laboratory data: Cross-tabulation of the worst-case abnormalities**

Cross-tabulation per lab test category (hematology, biochemistry and coagulation) and lab test. Each lab test will begin on a new page. The table will present the shift in abnormality (L/N/H/L+H) at the worst post-baseline time point versus the baseline abnormality (L/N/H).

Tests without normal ranges will not be presented in this table.

Population: safety population.

## 16.6 Safety: Vital Signs

### **Table 14.3.3.1: Vital signs: Descriptive statistics of the actual values and change from baseline per time point**

Descriptive statistics per test and time point. Table sorted first by treatment group, then by time point. Each test will begin on a new page.

Population: safety population.

### **Table 14.3.3.2: Vital signs: Descriptive statistics of the percent change from baseline per time point**

Descriptive statistics per test and time point. Table sorted first by treatment group, then by time point. Each test will begin on a new page.

Population: safety population.

## 16.7 Pharmacodynamics

### **Table 14.4.1.1: Krebs von den Lungen (KL-6) biomarker - Actual values**

Descriptive statistics of KL-6 concentrations (actual values) per timepoint.

Part 1 : Modified intent-to-treat population.  
Part 2 : RSV infected population

**Table 14.4.1.2: Krebs von den Lungen (KL-6) biomarker - Change from baseline.**

Descriptive statistics of KL-6 concentrations (change from baseline) per timepoint.

Part 1 : Modified intent-to-treat population.  
Part 2 : RSV infected population

**Table 14.4.1.3: Krebs von den Lungen (KL-6) biomarker - Percent change from baseline.**

Descriptive statistics of KL-6 concentrations (percent change from baseline) per timepoint.

Part 1 : Modified intent-to-treat population.  
Part 2 : RSV infected population

## 16.8 Immunogenicity

**Table 14.5.1.1: Immunogenicity: incidence of TE ADA status and pre-Ab status based on ADA assay results**

Table sorted by treatment group.

The table will present the incidence of different subject categories based on the pre-Ab status versus the treatment-emergent ADA status.

Population: safety population.

**Table 14.5.1.2: Immunogenicity: Incidence of pre-dose NAb status and TE NAb status based on NAb assay result**

Table sorted by treatment group.

The table will present the incidence of different subject categories based on the pre-dose status versus the treatment-emergent NAb status.

Population: safety population.

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Population: safety population.

**Table 14.5.1.4: Immunogenicity: Drug concentrations by ADA subject classification**

Descriptive statistics of drug concentrations by treatment group and by scheduled sampling time and by a subset of ADA subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos). In case the actual sampling time deviates more than allowed per study protocol from the nominal time, these samples will not be included in the calculation of descriptive statistics on pharmacokinetic concentrations and a footnote will be added to the table.

No ALX-0171 total will be presented in this table.

Population: Subjects that have extensive PK sampling .

**Table 14.5.1.5: Immunogenicity: mean change from baseline (to Day 2, 5 hours post dose) in Global Severity Score (GSS) by ADA subject classification**

Descriptive statistics of mean change from baseline (to Day 2, 5 hours post dose) in GSS by a subset of ADA subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos,).

Population: Safety population.

**Table 14.5.1.6: Immunogenicity: Viral load (time to BQL, Plaque assay) by ADA subject classification**

Kaplan-Meier analysis The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs by a subset of ADA subject categories (Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos,

Population: Safety population.

**Table 14.5.1.7: Immunogenicity: Drug concentrations by NAb subject classification**

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No ALX-0171 total will be presented in this table.

Population: Subjects that have extensive PK sampling .

**Table 14.5.1.8: Immunogenicity: mean change from baseline (to Day 2, 5 hours post dose) in Global Severity Score (GSS) by NAb subject classification**

Descriptive statistics of mean change from baseline (to Day 2, 5 hours post dose) in GSS by a subset of NAb category (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment).

Population: Safety Population

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Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs by a subset of NAb category (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment)

Population: Safety population.



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Part 1: BSL to day 3

Part 2: BSL to FU including only the pre-dose assessments for the first 3 days

Population: mITT population.

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Part 1: BSL to day 3

Part2: BSL to FU including only the pre-dose assessments for the first 3 days

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Population: mITT.

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Population: mITT population.

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Population: mITT.

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Population: mITT population.

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Population: RSV infected population.

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Population: RSV infected population.

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Population: RSV infected population.

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Population: mITT population.

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Mean time profile, showing the mean values (with SE) for each treatment group at each scheduled time point.

Population: mITT population.

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Population: mITT population.

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Bar chart of mean actual values per treatment group (different adjacent bars for treatment) over time (groups of adjacent bars represent consecutive timepoints). Stacked parts of bar represent individual items. Figure will consist of 2 parts:

Part 1: BSL to day 3

Part 2: BSL to FU including only the pre-dose assessments for the first 3 days

Population: mITT population.

**Figure 14.2.5.3: Respiratory Distress Assessment Instrument (RDAI) change from from baseline – Mean(SE) plot.**

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Population: mITT population.

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Population: mITT population.

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Population: mITT population.

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Population: mITT population.

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### 17.4 Safety: Laboratory

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### 17.5 Safety: Vital Signs

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## 17.6 Pharmacodynamics

### Figure 14.6.1.1: Krebs von den Lungen (KL-6) biomarker - Actual values – Mean(SE) Plot-

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Population: mITT.

### Figure 14.6.1.2: Krebs von den Lungen (KL-6) biomarker – Change from baseline – Mean(SE) Plot

Mean time profile, showing the (arithmetic) mean change from baseline (with SE) for each treatment group at each scheduled time point.

Population: mITT.

## 17.7 Immunogenicity

### Figure 14.7.1.1: Immunogenicity: Scatterplot of PK concentrations by ADA subject classification

For each treatment group separately, scatterplot of the PK concentrations vs. time, with a subset of ADA subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) represented by different plotting symbols. Y-axis scales can be independent per treatment group to allow better interpretation of the results. Nominal sampling times are used unless the actual time deviates more than allowed per study protocol. In that case the actual time is used.

Population: Subjects that have extensive PK sampling .

### Figure 14.7.1.2: Immunogenicity: Mean(SE) plot of PK concentrations by ADA subject classification

For each treatment group separately, line plot of the mean PK concentrations, including SE bars, with one line per subset of ADA subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos). Y-axis scales can be independent per treatment group to allow better interpretation of the results. Nominal sampling times are used unless the actual time deviates more than allowed per study protocol. In the latter case, these samples will not be included in the calculation of the mean pharmacokinetic concentrations and a footnote will be added to the figure.

Population: Subjects that have extensive PK sampling .

### Figure 14.7.1.3: Immunogenicity: Scatterplot of change from baseline (to Day 2,5 hours post dose) in GSS by ADA subject classification

For each treatment group separately, scatterplot of the mean change from baseline in GSS score, with a subset of ADA subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) represented by different plotting symbols. Y-axis scales can be independent per treatment group to allow better interpretation of the results.

Population: safety population.

**Figure 14.7.1.4: Immunogenicity: Kaplan Meier plot of viral load (time to BQL) by ADA subject classification**

For each treatment group separately, KM plot by subset of ADA subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) represented by different plotting symbols.

Population: safety population.

**Figure 14.7.1.5: Immunogenicity: Scatterplot of PK concentrations by NAb subject classification**

For each treatment group separately, scatterplot of the PK concentrations vs. time, with a subset of NAb subject categories (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment) represented by different plotting symbols. Y-axis scales can be independent per treatment group to allow better interpretation of the results. Nominal sampling times are used unless the actual time deviates more than allowed per study protocol. In that case the actual time is used.

Population: Subjects that have extensive PK sampling .

**Figure 14.7.1.6: Immunogenicity: Scatterplot of change from baseline (to Day 2,5 hours post dose) in GSS by NAb subject classification**

For each treatment group separately, scatterplot of the mean change from baseline in GSS score, with a subset of NAb subject categories ((Total Pre-Ab Neg, Total Pre-Ab Pos, Total TE ADA Neg and Total TE ADA Pos) represented by different plotting symbols. Y-axis scales can be independent per treatment group to allow better interpretation of the results.

Population: safety population.

**Figure 14.7.1.7: Immunogenicity: Kaplan Meier plot of viral load (time to BQL) by NAb subject classification**

For each treatment group separately, KM plot by subset of NAb subject categories (Total Pre-dose Neg, Total Pre-dose Pos, Total Neg on treatment and Total Pos on treatment) represented by different plotting symbols.

Population: safety population.

## 18 INDEX OF LISTINGS

### 18.1 General

**Listing 16.2.1.1: Subject disposition: Allocation**

Listing of randomization numbers, subject numbers, randomization groups, and treatment(s) received.

Listing sorted by randomization number. Population indicators, date of randomization, country and investigator are on this list as well. All discrepancies (as-randomized versus as-treated) will be flagged.

Population: ITT population.

**Listing 16.2.1.2: Subject disposition: Code-breaking information**

Listing of the code-breaking information. Only subjects for which the code was broken are presented in this listing.

Population: ITT population.

**Listing 16.2.1.3: Treatment and trial termination**

Listing of the reason for completion/discontinuation and the number of days since first study drug administration. In case the discontinuation was due to AE, the AE will be presented in this listing. If there is another explanation on the discontinuation reason collected in the CRF, this will also be presented in this listing.

Population: ITT population.

**Listing 16.2.1.4: Visit listing**

Listing of all the visits performed by subject and timepoint. This listing will be based on the SV domain.

Population: ITT population.

**Listing 16.2.1.5: Major Protocol deviations**

Listing of all major protocol deviations including category (DVDECOD) and description. PDs contributing to exclusion from the Per protocol analysis population will be flagged.

Population: mITT population .

**Listing 16.2.1.6: Screening failures**

Listing of screening failures.

The trial termination reason and/or the reason for being a no-treatment subject or a non-randomized subject will be listed, whichever is available.

Population: all screened population, minus the ITT population.

**Listing 16.2.2.1: Demographic data**

Listing of all demographic parameters and date of informed consent(s).

Population: mITT population.

**Listing 16.2.2.2: Baseline disease characteristics**

Listing of all baseline disease characteristics.

Population: mITT population.

**Listing 16.2.2.3: Viral screening tests**

Listing of all viral screening tests.

Population: mITT population.

**Listing 16.2.2.4: Medical history**

Listing of the medical history data findings available in the CRF

Population: mITT population.



**Listing 16.2.2.5: Previous and concomitant therapies**

Listing of all data on previous and concomitant therapies, including coding information.

Population: safety population.

**Listing 16.2.2.6: Exposure to study medication: Actual data**

Listing of all data collected in the CRF related to the use of medication.

Population: safety population.

**Listing 16.2.2.7: Exposure to study medication: Compliance**

Listing of calculated compliance.

Population: safety population.

**Listing 16.2.2.8: Comments**

Listing of remarks and comments written in the CRF.

Population: ITT population.

## 18.2 Efficacy

**Listing 16.2.3.1: Primary Endpoint - time to below quantification limit in RSV viral load (plaque assay) - Product limit survival estimates.**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Population: mITT population

**Listing 16.2.3.2: Sensitivity analysis - time to below quantification limit in RSV Viral load (plaque assay)- RSV infected population - product limit survival estimates.**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Population: RSV infected population

**Listing 16.2.3.3: Sensitivity analysis - time to below quantification limit in RSV viral load (plaque assay) - Per Protocol analysis - product limit survival estimates.**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Population: Per Protocol population

**Listing 16.2.3.4: Time to below quantification limit in RSV viral load (RT-qPCR assay) - Product limit survival estimates.**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Part 1: mITT population

Part 2 : RSV-infected population

**Listing 16.2.3.5: Time to undetectability of RSV viral load (plaque assay) - Product limit survival estimates.**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Part 1: mITT population

Part 2 : RSV-infected population

**Listing 16.2.3.6: Time to undetectability of RSV viral load (RT-qPCR assay) - Product limit survival estimates.**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Part 1: mITT population

Part 2 : RSV-infected population

**Listing 16.2.3.7: Global Severity score**

Listing per subject and time point of GSS subscores and total score (actual and change from baseline). Imputed values will be flagged in the listing.

Population: mITT population.

**Listing 16.2.3.8: Viral Load**

Listing per subject and time point of RSV viral load (plaque assay and RT-qPCR), including time to BQL and time weighted average change from baseline. Population flag for RSV infected population will be included

Population: mITT population

**Listing 16.2.3.9: Time to Clinical response - Adequate oxygen saturation and oral feeding - Product limit survival estimates**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Population: mITT population

**Listing 16.2.3.10: Time to Clinical response - Adequate oxygen saturation - Product limit survival estimates**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Population: mITT population

**Listing 16.2.3.11: Time to Clinical response - Adequate oral feeding - Product limit survival estimates**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis

Population: mITT population

**Listing 16.2.3.12: Clinical response**

Listing per subject and time point of clinical response (adequate oxygen supply and oral feeding). Timepoint of single and combined will be flagged.

Population: mITT population.

**Listing 16.2.3.13: Clinical symptoms – Respiratory rate and body temperature**

Listing per subject and time point of clinical symptoms

Population: mITT population.

**Listing 16.2.3.14: Clinical symptoms - Feeding**

Listing per subject and time point of clinical symptoms

Population: mITT population.

**Listing 16.2.3.15: Clinical symptoms – Respiratory distress**

Listing per subject and time point of clinical symptoms  
Population: mITT population.

**Listing 16.2.3.16: Clinical symptoms - Cough**

Listing per subject and time point of clinical symptoms  
Population: mITT population.

**Listing 16.2.3.17: Clinical symptoms – General appearance**

Listing per subject and time point of general appearance  
Population: mITT population.

**Listing 16.2.3.18: RDAI and RACS**

Listing per subject and time point of RDAI subscore items and total scores and RACS score.  
Imputed values will be flagged in the listing.  
Population: mITT population.

**Listing 16.2.3.19: Length of hospital stay – Product limit survival estimates**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis  
Population: mITT population

**Listing 16.2.3.20: Time between first dose and hospital discharge – Product limit survival estimates**

Listing of product limit survival estimates from the corresponding Kaplan Meier analysis  
Population: mITT population

**Listing 16.2.3.21: Hospitalization**

Listing per subject and time point of length of hospital stay, oxygen therapy and ICU stay  
Population: mITT population.

**Listing 16.2.3.22: Oxygen supply**

Listing per subject and time point of oxygen supply.  
Population: mITT population.

**Listing 16.2.3.23: Feeding support**

Listing per subject and time point of feeding support.  
Population: mITT population.

**Listing 16.2.3.24: Parent /Caregiver assessment of clinical condition**

Listing per subject and time point of Parent /Caregiver assessment  
Population: mITT population.

**Listing 16.2.3.25: Apnea and ventilation**

Listing per subject and time point of apnea and ventilation data  
Population: mITT population.

### 18.3 Safety: Adverse Events

#### Listing 16.2.4.1: Adverse events

Listing of all events of the following:

Date(time) of nebulization

- AE preferred term (flagging serious TEAEs with an asterisk \*)
- AE start and end
- AE onset day
- AE duration
- AE severity
- AE drug relatedness
- AE study procedure
- AE outcome
- AE action taken
- Concomitant therapy started (yes/no)

In such a way that all information fits on one line for each AE.

Population: safety population.

#### Listing 16.2.4.2: Adverse events: Serious adverse events

Same as the previous listing, but only selecting SAEs (irrespective their treatment-emergence). Additionally, the reason(s) for SAE will be listed as well. Along with ADA (log<sub>10</sub>titer), if measured. If not, mention N/A.

Population: safety population.

#### Listing 16.2.4.3: Adverse events leading to discontinuation

Same as the previous listing, but only selecting TEAEs that lead to a stop of trial medication.

Population: safety population.

#### Listing 16.2.4.4: Adverse events leading to death

Same as the previous listing, but only selecting adverse events leading to death (irrespective their treatment-emergence).

### 18.4 Safety: Physical examination

#### Listing 16.2.4.5: Physical examinations: Abnormalities

Listing of all abnormal findings, including the clinically significance status.

Population: safety population.

### 18.5 Safety: Laboratory

**Listing 16.2.5.1: Laboratory data: Full listing**

Listing of all data. Comments are not included in this listing but are presented in a separate listing.

Population: safety population.

**Listing 16.2.5.2: Laboratory data: Abnormalities**

Listing of all data scored as out-of-normal-range or clinically significant, plus also the baseline reference time point. Comments are not included in this listing but are presented in a separate listing.

Population: safety population.

**Listing 16.2.5.3: Laboratory data: Comments**

Listing of all comments. This listing will be linked to the Full listing and the Abnormalities listing via numbered entries like “[C13]”.

Population: safety population.

**18.6 Safety: Vital Signs****Listing 16.2.6.1: Vital signs: Full listing**

Listing of all data.

Population: safety population.

**Listing 16.2.6.2: Vital signs: Comments**

Listing of all comments. This listing will be linked to the Full listing via numbered entries like “[C13]”.

Population: safety population

**18.7 Pharmacokinetics****Listing 16.2.7.1: Pharmacokinetics: Full listing**

Listing of all data.

Population: safety population.

**18.8 Pharmacodynamics****Listing 16.2.8.1: PD: Individual KL-6 concentrations**

Listing of all individual KL-6 values.

Population: mITT population

## 18.9 Immunogenicity

### Listing 16.2.9.1: Immunogenicity: Full listing

Listing of all immunogenicity parameters (ADA log<sub>10</sub>(titer), NAb result (ratio value), at each time point. Listing of subject classification based on ADA assay, and listing of subject classification based on NAb assay with treatment for the classification indicated.

Population: safety population

19 APPENDICES

19.1 Appendix A: Time and events Schedule

19.1.1 Time and events Schedule V1.0

Period Visit	Screening <sup>a</sup>	Study Drug Treatment Period <sup>b</sup>												n-hospital Treatment Period C	Post FU visit (Day 14±2) or Withdrawal visit <sup>d</sup>	EOSD (Day 28±2)	
		Hospitalized Dosing						Hospitalized Ambulatory Dosing									
		Day 1			Day 2			Day 3			Day 3						
Approximate time/ Study procedure	24h randomization	to 2h dose	to Dose	2h Dose	5h ±1h)	2h to dose	Dose	2h Dose	5h (±1h)	2h to dose	Dose	2h Dose	5h <sup>u</sup> (+2h)	Morning and evening			
Informed consent	X																
Inclusion/exclusion criteria	X																
RSV diagnosis <sup>e</sup>	X																
Demographics and medical history	X																
Randomization		X															
Hospitalization information/Clinical response information <sup>f</sup>																	→
Study drug administration <sup>g</sup>			X				X				X						
Nasal mid-turbinate swab <sup>h</sup>		X			X	X			X	X		X		xi	X		X
Physical examination <sup>j</sup>	X	X			X	X			X	X		X	X	X	X		X
Body weight	X															X	X
Body height	X																
Body temperature	X	X			X	X			X	X		X		X	X		
SpO <sub>2</sub> <sup>k</sup>	X	X		X	X	X		X	X	X		X	X	X			
Heart rate	X	X		X	X	X		X	X	X		X	X	X		X	
Feeding <sup>l</sup>	X	X			X	X			X	X		X		X		X	
General appearance	X	X			X	X			X	X		X		X		X	
Lung auscultation <sup>m</sup>	X	X		X	X	X		X	X	X		X	X	X		X	X
(Respiratory muscle) retractions	X	X		X	X	X		X	X	X		X		X		X	
Respiratory rate	X	X		X	X	X		X	X	X		X	X	X		X	

Period Visit	Screening a	Study Drug Treatment Period b												n-hospital Post-Treatment Period C	FU visit (Day 14±2) or Withdrawal visit d	EOSC (Day 28±2)
		Hospitalized Dosing						Hospitalized Ambulatory Dosing e								
		Day 1				Day 2				Day 3						
Approximate time/ Study procedure	24h randomization	2h to dose	2h to Dose	2h 5h ±1h)	2h to dose	Dose	2h 5h ±1h)	2h to dose	Dose	2h 5h ±1h)	5h u (+2h)	Morning and evening				
Daytime coughing	X	X		X	X	X		X	X	X		X	X	X	X	
(Sleep disturbance from) night-time coughing n	xn	xn				xn						xn		xn	x	
Parent/caregiver assessment O															→	
Pharmacokinetics (single sample)								←			→					
Pharmacokinetics (more extensive sampling)					xq			←	q	→	←					
Clinical laboratory (hematology and clinical biochemistry)	xr													xS		
Immunogenicity	xr													xS		
Previous and concomitant medication															→	
Adverse events t															→	

h = hour; FU = Follow-up; EOS = End of Study.

**Timing of assessments:** post-dose time points relate to the end of the 2<sup>nd</sup> of the 2 nebulizations of study drug administration. Pre-dose time points relate to the start of the 1<sup>st</sup> of the 2 nebulizations of study drug administration. Throughout the study, study personnel should make every reasonable effort to follow the timing in the schedule of assessments for each subject.

- a. If the Day 1 pre-dose assessments are performed within 2 hours after the screening assessments have been performed, the assessments already done at screening do not need to be repeated and only the additional assessments to be performed on Day 1, pre-dose will need to be performed.
- b. Study drug administration should take place within 24 hour intervals (± 4 hours) relative to the start of the 1<sup>st</sup> nebulization of the 1<sup>st</sup> dose. Provided that the clinical response criteria have been met, discharge from the hospital can take place per protocol at the Investigator’s discretion from dosing Day 2 onwards after all required assessments of the 5 hours (± 1 hour) post-dose time point have been completed. Subjects who started study drug dosing but were discontinued prematurely from study drug treatment, should be further monitored according to the in-hospital post treatment period (if applicable) and should attend the FU and EOS visits.
- c. The in-hospital post-treatment assessments are to be performed for subjects who are not discharged from the hospital after the completion or discontinuation of study drug treatment.
- d. For subjects who discontinue the study before Day 28, the Withdrawal visit will be conducted on the day of withdrawal as long as there has been no withdrawal of consent. If the Withdrawal visit assessments are performed within 6 hours after the Day 1, Day 2, Day 3, or in-hospital post-treatment Day assessments have been performed, the assessments already done at the prior time point do not need to be repeated and only the additional assessments to be performed on the Withdrawal Visit will need to be performed. No EOS visit needs to be performed after the Withdrawal Visit. In case subjects are hospitalized beyond the Day 14 FU visit, the additional assessments (in addition to the in-hospital post treatment period assessments) of the Day 14 FU visit need to be done on Day 14.
- e. RSV infection will be confirmed either according to routine site practice (PCR or diagnostic quick test), or using a (Sponsor-provided) commercial kit.
- f. Hospitalization information will include occurrence of ICU transfer, apnea episodes, initiation and type of ventilation and hospital/ICU discharge information. Assessment of Clinical Response will be done with collection of date and time of adequate oral feeding to enable discharge as well as adequate oxygen saturation on room air of >92% over a period of 4 hours.



- g. Study drug will be administered via nebulization using the study-specific device. One dose consists of 2 serial nebulizations.
- h. A mid-turbinal nasal swab should be taken using provided kits and following specific instructions in case the subject is re-hospitalized or consults the Investigator for a respiratory condition after hospital discharge.
- i. A nasal swab should only be collected during the in-hospital post-treatment period on the day of hospital discharge.
- j. Physical examination includes examination of abdomen and skin and ears/nose/throat. Lung auscultation is listed separately as it is to be assessed more frequently.
- k. Continuous monitoring of SpO<sub>2</sub> needs to be done until the clinical response criterion for oxygen has been met and/or in case saturation monitoring is to be continued according to the Investigator's judgment.
- l. Type of feeding support, if any, and feasibility of oral feeding.
- m. To assess wheezing, crackles/crepitation and other abnormalities in lung auscultation.
- n. Sleep disturbance from night-time coughing to be documented pre-dose the next day, or at the FU visit, EOS or Withdrawal visit, based on feedback from the nursing staff. In case there is no night between screening and study drug administration on Day 1, the Day 1 assessment should not be performed.
- o. The parent/caregiver assessment should be done every evening from screening until the EOS visit by completing a diary.
- p. Blood draw for PK assessments on Day 2 or Day 3, at any time between 0.5 hours post second dose and start of the third dose. If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.
- q. 48 subjects will undergo more extensive PK analysis (3 PK samples per subject instead of the 1 sample), i.e., blood draws on Days 2-3 1) pre second dose, 2) at any time between 0.5 hours and 3 hours post second dose, and 3) at any time between 3 hours and 6 hours post second dose (and at least 1 hour apart from the previous sampling); If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.
- r. Blood draw at screening for clinical laboratory (hematology and clinical biochemistry) and immunogenicity. If sufficient serum remains after immunogenicity assessment, exploratory biomarker (KL-6) may also be evaluated. In case the blood sample for immunogenicity was not taken at screening, the sample should be collected at the Day 1 pre-dose timepoint, as far as possible.
- s. Blood draw on Day 14 for clinical laboratory (hematology and clinical biochemistry) and immunogenicity. If sufficient serum remains after immunogenicity assessment, exploratory biomarker (KL-6) may also be evaluated. No blood sample needs to be taken in case of premature withdrawal from the study for subjects who did not receive any study drug. In case the blood sample for immunogenicity was not taken on Day 14, the sample should be collected at the EOS (Day 28) visit, as far as possible.
- t. In case of a severe and/or serious hypersensitivity reaction, an additional serum sample should be collected (if reasonably feasible) as soon as possible after the start of the event.
- u. For Day 3, the 5 hour post dose assessments are only applicable for sites in Germany.

### 19.1.2 Time and events Schedule V2.0

Period	Screening <b>a</b>	Study Drug Treatment Period <b>b</b>											In-hospital Post-Treatment Period <b>c</b>	FU visit (Day 14±2) or Withdrawal visit <b>d</b>	EOS <b>d</b> (Day 28±2)	
		Hospitalized Dosing									Hospitalized Ambulatory Dosing					
		Day 1			Day 2			Day 3			Morning and evening					
Approximate time/ Study procedure	-24h to randomization	-2h to dose	Dose	2h	5h (±1h)	-2h to dose	Dose	2h	5h (±1h)	-2h to dose	Dose	2h				
Informed consent	X															
Inclusion/exclusion criteria	X															
RSV diagnosis <b>e</b>	X															

Period  Visit	Screening <b>a</b>	Study Drug Treatment Period <b>b</b>										In-hospital Post-Treatment Period <b>c</b>  Morning and evening	FU visit (Day 14±2) or Withdrawal visit <b>d</b>	EOS <b>d</b> (Day 28±2)		
		Hospitalized Dosing					Hospitalized or Ambulatory Dosing									
		Day 1			Day 2			Day 3								
Approximate time/ Study procedure	-24h to randomization	-2h to dose	Dose	2h	5h (±1h)	-2h to dose	Dose	2h	5h (±1h)	-2h to dose	Dose	2h				
Demographics and medical history	X															
Randomization		X														
Hospitalization information/Clinical response information <b>f</b>																→
Study drug administration <b>g</b>			X				X				X					
Nasal mid-turbinate swab <b>h</b>		X			X	X			X	X		X	X	X	X	
Physical examination <b>j</b>	X	X			X	X			X	X		X		X	X	X
Body weight	X														X	X
Body height	X															
Body temperature	X	X			X	X			X	X		X		X	X	
SpO <sub>2</sub> <b>k</b>	X	X		X	X	X		X	X	X		X		X		
Heart rate	X	X		X	X	X		X	X	X		X		X	X	
Feeding <b>l</b>	X	X			X	X			X	X		X		X	X	
General appearance	X	X			X	X			X	X		X		X	X	
Lung auscultation <b>m</b>	X	X		X	X	X		X	X	X		X		X	X	X
(Respiratory muscle) retractions	X	X		X	X	X		X	X	X		X		X	X	
Respiratory rate	X	X		X	X	X		X	X	X		X		X	X	
Daytime coughing	X	X		X	X	X		X	X	X		X		X		X
(Sleep disturbance from) night-time coughing <b>n</b>	xn	xn				xn				xn				xn	xn	X
Parent/caregiver assessment <b>o</b>																→
Pharmacokinetics (single sample)																←p→
Pharmacokinetics (more extensive sampling)						xq										←q→
Clinical laboratory (hematology and clinical biochemistry)	xr														xS	
Immunogenicity	xr														xS	
Previous and concomitant medication																→

Period  Visit	Screening <b>a</b>	Study Drug Treatment Period <b>b</b>										In-hospital Post-Treatment Period <b>c</b>  Morning and evening	FU visit (Day 14±2) or Withdrawal visit <b>d</b>	EOS <b>d</b> (Day 28±2)	
		Hospitalized Dosing								Hospitalized or Ambulatory Dosing					
		Day 1			Day 2			Day 3							
Approximate time/ Study procedure	-24h to randomization	-2h to dose	Dose	2h	5h (±1h)	-2h to dose	Dose	2h	5h (±1h)	-2h to dose	Dose	2h			
Adverse events †															

h = hour; FU = Follow-up; EOS = End of Study.

**Timing of assessments:** post-dose time points relate to the end of the 2nd of the 2 nebulizations of study drug administration. Pre-dose time points relate to the start of the 1st of the 2 nebulizations of study drug administration. Throughout the study, study personnel should make every reasonable effort to follow the timing in the schedule of assessments for each subject.

- a. If the Day 1 pre-dose assessments are performed within 2 hours after the screening assessments have been performed, the assessments already done at screening do not need to be repeated and only the additional assessments to be performed on Day 1, pre-dose will need to be performed.
- b. Study drug administration should take place within 24 hour intervals (± 4 hours) relative to the start of the 1st nebulization of the 1st dose. Provided that the clinical response criteria have been met, discharge from the hospital can take place per protocol at the Investigator’s discretion from dosing Day 2 onwards after all required assessments of the 5 hours (± 1 hour) post-dose time point have been completed. Subjects who started study drug dosing but were discontinued prematurely from study drug treatment, should be further monitored according to the in-hospital post treatment period (if applicable) and should attend the FU and EOS visits.
- c. The in-hospital post-treatment assessments are to be performed for subjects who are not discharged from the hospital after the completion or discontinuation of study drug treatment.
- d. For subjects who discontinue the study before Day 28, the Withdrawal visit will be conducted on the day of withdrawal as long as there has been no withdrawal of consent. If the Withdrawal visit assessments are performed within 6 hours after the Day 1, Day 2, Day 3, or in-hospital post-treatment Day assessments have been performed, the assessments already done at the prior time point do not need to be repeated and only the additional assessments to be performed on the Withdrawal Visit will need to be performed. No EOS visit needs to be performed after the Withdrawal Visit. In case subjects are hospitalized beyond the Day 14 FU visit, the additional assessments (in addition to the in-hospital post treatment period assessments) of the Day 14 FU visit need to be done on Day 14.
- e. RSV infection will be confirmed either according to routine site practice (PCR or diagnostic quick test), or using a (Sponsor-provided) commercial kit.
- f. Hospitalization information will include occurrence of ICU transfer, apnea episodes, initiation and type of ventilation and hospital/ICU discharge information. Assessment of Clinical Response will be done with collection of date and time of adequate oral feeding to enable discharge as well as adequate oxygen saturation on room air of >92% over a period of 4 hours.
- g. Study drug will be administered via nebulization using the study-specific device. One dose consists of 2 serial nebulizations.
- h. A mid-turbinal nasal swab should be taken using provided kits and following specific instructions in case the subject is re-hospitalized or consults the Investigator for a respiratory condition after hospital discharge.
- i. A nasal swab should only be collected during the in-hospital post-treatment period on the day of hospital discharge.
- j. Physical examination includes examination of abdomen and skin and ears/nose/throat. Lung auscultation is listed separately as it is to be assessed more frequently.
- k. Continuous monitoring of SpO2 needs to be done until the clinical response criterion for oxygen has been met and/or in case saturation monitoring is to be continued according to the Investigator’s judgment.
- l. Type of feeding support, if any, and feasibility of oral feeding.
- m. To assess wheezing, crackles/crepitation and other abnormalities in lung auscultation.
- n. Sleep disturbance from night-time coughing to be documented pre-dose the next day, or at the FU visit, EOS or Withdrawal visit, based on feedback from the nursing staff. In case there is no night between screening and study drug administration on Day 1, the Day 1 assessment should not be performed.

- <sup>a</sup>. The parent/caregiver assessment should be done every evening from screening until the EOS visit by completing a diary.
- <sup>p</sup>. Blood draw for PK assessments on Day 2 or Day 3, at any time between 0.5 hours post second dose and start of the third dose. If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.
- <sup>q</sup>. 48 subjects will undergo more extensive PK analysis (3 PK samples per subject instead of the 1 sample), i.e., blood draws on Days 2-3 1) pre second dose, 2) at any time between 0.5 hours and 3 hours post second dose, and 3) at any time between 3 hours and 6 hours post second dose (and at least 1 hour apart from the previous sampling); If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.
- <sup>r</sup>. Blood draw at screening for clinical laboratory (hematology and clinical biochemistry) and immunogenicity. If sufficient serum remains after immunogenicity assessment, exploratory biomarker (KL-6) may also be evaluated. In case the blood sample for immunogenicity was not taken at screening, the sample should be collected at the Day 1 pre-dose timepoint, as far as possible.
- <sup>s</sup>. Blood draw on Day 14 for clinical laboratory (hematology and clinical biochemistry) and immunogenicity. If sufficient serum remains after immunogenicity assessment, exploratory biomarker (KL-6) may also be evaluated. No blood sample needs to be taken in case of premature withdrawal from the study for subjects who did not receive any study drug. In case the blood sample for immunogenicity was not taken on Day 14, the sample should be collected at the EOS (Day 28) visit, as far as possible.
- <sup>t</sup>. In case of a severe and/or serious hypersensitivity reaction, an additional serum sample should be collected (if reasonably feasible) as soon as possible after the start of the event.

### 19.1.3 Time and events Schedule V3.0

Period Visit	Screening <b>a, b</b>	Study Drug Treatment Period <b>C</b>											In-hospital Post-Treatment Period <b>d</b>	FU visit (Day 14±2) or Withdrawal visit <b>e</b>	EOS <b>e</b> (Day 28±2)
		Hospitalized Dosing								Hospitalized or Ambulatory Dosing					
		Day 1			Day 2			Day 3			Morning and evening				
Approximate time/ Study procedure	-24h to randomization	-3h to dose	Dose	2h (±0.5h)	5h (±1h)	-2h to dose	Dose	2h (±0.5h)	5h (±1h)	-2h to dose		Dose	2h (±0.5h)		
Informed consent	X														
Inclusion/exclusion criteria	X														
RSV diagnosis <b>f</b>	X														
Demographics and medical history	X														
Hospitalization information/Clinical response information <b>g</b>															→
Study drug administration <b>h</b>				X			X				X				
Nasal mid-turbinate swab <b>i</b>		X			X	X			X	X		X	xj	X	
Physical examination <b>k</b>	X	X			X	X			X	X		X	X	X	X
Body weight	X													X	X
Body height	X														
Body temperature	X	X			X	X			X	X		X	X	X	
General appearance	X	X			X	X			X	X		X	X	X	



Period  Visit	Screening a, b	Study Drug Treatment Period C											In-hospital Post-Treatment Period d	FU visit (Day 14±2) or Withdrawal visit e	EOS e (Day 28±2)	
		Hospitalized Dosing									Hospitalized or Ambulatory Dosing					
		Day 1			Day 2			Day 3			Morning and evening					
Approximate time/ Study procedure	-24h to randomization	-3h to dose	Dose	2h (±0.5h)	5h (±1h)	-2h to dose	Dose	2h (±0.5h)	5h (±1h)	-2h to dose	Dose	2h (±0.5h)				
Lung auscultation n	X	X		X	X	X		X	X	X		X	X	X	X	X
Heart rate	X	X		X	X	X		X	X	X		X	X	X	X	
SpO <sub>2</sub> l	X	X		X	X	X		X	X	X		X	X	X		
Feeding m	X	X			X	X			X	X		X	X	X	X	
(Respiratory muscle) retractions	X	X		X	X	X		X	X	X		X	X	X	X	
Respiratory rate	X	X		X	X	X		X	X	X		X	X	X	X	
Randomization b		X														
Daytime coughing	X	X		X	X	X		X	X	X		X	X	X	X	X
(Sleep disturbance from) night-time coughing o	xO	xO				xO				xO				xO	xO	X
Parent/caregiver assessment p																→
Pharmacokinetics (single sample)																←→q
Pharmacokinetics (more extensive sampling)						xr										←→r→←
Clinical laboratory (hematology and clinical biochemistry)	xS, t														xU	
Immunogenicity	xS														xU	
Previous and concomitant medication																→
Adverse events V																→

h = hour; FU = Follow-up; EOS = End of Study.

**Timing of assessments:** post-dose time points relate to the end of the 2nd of the 2 nebulizations of study drug administration. Pre-dose time points relate to the start of the 1st of the 2 nebulizations of study drug administration. Throughout the study, study personnel should make every reasonable effort to follow the timing in the schedule of assessments for each subject.

- a. If the Day 1 pre-dose assessments will be performed within 3 hours after the screening assessments have been performed, the assessments already done at screening do not need to be repeated and only the additional assessments to be performed on Day 1, pre-dose will need to be performed.
- b. At the time of randomization, subjects should be eligible for study participation as defined in the inclusion/exclusion criteria. Therefore, at a minimum, the SpO<sub>2</sub>, feeding, respiratory muscle retractions, and respiratory rate should be evaluated on Day 1 before randomization, unless these assessments were already performed within the last 3 hours before randomization.
- c. Study drug administration should take place within 24 hour intervals (± 4 hours) relative to the start of the 1st nebulization of the 1st dose. Provided that the clinical response criteria have been met, discharge from the hospital can take place per protocol at the Investigator's discretion from dosing Day 2 onwards after all required assessments of the 5 hours (± 1 hour) post-dose time

- point have been completed. Subjects who started study drug dosing but were discontinued prematurely from study drug treatment, should be further monitored according to the in-hospital post treatment period (if applicable) and should attend the FU and EOS visits.
- d. The in-hospital post-treatment assessments are to be performed for subjects who are not discharged from the hospital after the completion or discontinuation of study drug treatment.
  - e. For subjects who discontinue the study before Day 28, the Withdrawal visit will be conducted on the day of withdrawal as long as there has been no withdrawal of consent. If the Withdrawal visit assessments are performed within 6 hours after the Day 1, Day 2, Day 3, or in-hospital post-treatment Day assessments have been performed, the assessments already done at the prior time point do not need to be repeated and only the additional assessments to be performed on the Withdrawal Visit will need to be performed. No EOS visit needs to be performed after the Withdrawal Visit. In case subjects are hospitalized beyond the Day 14 FU visit, the additional assessments (in addition to the in-hospital post treatment period assessments) of the Day 14 FU visit need to be done on Day 14.
  - f. RSV infection will be confirmed either according to routine site practice (PCR or diagnostic quick test), or using a (Sponsor-provided) commercial kit.
  - g. Hospitalization information will include occurrence of ICU transfer, apnea episodes, initiation and type of ventilation and hospital/ICU discharge information. Assessment of Clinical Response will be done with collection of date and time of adequate oral feeding to enable discharge as well as adequate stable oxygen saturation on room air of >92% over a period of at least 4 hours.
  - h. Study drug will be administered via nebulization using the study-specific device. One dose consists of 2 serial nebulizations.
  - i. A mid-turbinal nasal swab should be taken using provided kits and following specific instructions in case the subject is re-hospitalized or consults the Investigator for a respiratory condition after hospital discharge.
  - j. A nasal swab should only be collected during the in-hospital post-treatment period on the day of hospital discharge.
  - k. Physical examination includes examination of abdomen and skin and ears/nose/throat. Lung auscultation is listed separately as it is to be assessed more frequently.
  - l. Continuous monitoring of SpO2 needs to be done until the clinical response criterion for oxygen has been met and/or in case saturation monitoring is to be continued according to the Investigator's judgment.
  - m. m. Type of feeding support, if any, and feasibility of oral feeding.
  - n. To assess wheezing, crackles/crepitation and other abnormalities in lung auscultation.
  - o. Sleep disturbance from night-time coughing to be documented pre-dose the next day or in the morning during the in-hospital post-treatment period, or at the FU visit, EOS or Withdrawal visit, based on feedback from the nursing staff. In case there is no night between screening and study drug administration on Day 1, the Day 1 assessment should not be performed.
  - p. The parent/caregiver assessment should be done every evening from screening until the EOS visit by completing a diary.
  - q. Blood draw for PK assessments on Day 2 or Day 3, at any time between 0.5 hours post second dose and start of the third dose. If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.
  - r. 48 subjects will undergo more extensive PK analysis (3 PK samples per subject instead of the 1 sample), i.e., blood draws on Days 2-3 1) pre second dose, 2) at any time between 0.5 hours and 3 hours post second dose, and 3) at any time between 3 hours and 6 hours post second dose (and at least 1 hour apart from the previous sampling); If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.
  - s. Blood draw at screening for clinical laboratory (hematology and clinical biochemistry) and immunogenicity. If sufficient serum remains after immunogenicity assessment, exploratory biomarker (KL-6) may also be evaluated. In case the blood sample for immunogenicity was not taken at screening, the sample should be collected at the Day 1 pre-dose timepoint, as far as possible.
  - t. If all hematology and biochemistry blood parameters required for the study are already known from analysis done as a routine assessment upon arrival at the hospital, collection of screening clinical laboratory samples does not need to be repeated for the purpose of this study. However, the samples should be analyzed at the same local laboratory that will be used for the remainder of the study.
  - u. Blood draw on Day 14 for clinical laboratory (hematology and clinical biochemistry) and immunogenicity. If sufficient serum remains after immunogenicity assessment, exploratory biomarker (KL-6) may also be evaluated. No blood sample needs to be taken in case of premature withdrawal from the study for subjects who did not receive any study drug. In case the blood sample for immunogenicity was not taken on Day 14, the sample should be collected at the EOS (Day 28) visit, as far as possible.
  - v. In case of a severe and/or serious hypersensitivity reaction, an additional serum sample should be collected (if reasonably feasible) as soon as possible after the start of the event.

**19.2 Appendix B: Concentration assessment plan**

**DRUG CONCENTRATION ASSESSMENT FROM COHORTS 1-3  
ALX0171-C201**

**A Randomized, Double-Blind, Placebo-Controlled, Multicenter Dose-Ranging Study of ALX-0171 in Infants and Young Children Hospitalized for Respiratory Syncytial Virus Lower Respiratory Tract Infection.**

**Note: This document will be added as an appendix to the Statistical Analysis Plan**

**Version: Final v1.0**

**Date: 21JUN 2017**

**Protocol: ALX0171-C201 Final version 2.0 – 25 OCT 2016**

**SIGNATURE PAGE**

The undersigned agree to the content outlined in this plan.

\_\_\_\_\_  
[REDACTED] (Date)  
Reporting Biostatistician  
[REDACTED]

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[REDACTED] (Date)  
Biostatistical Coordinator  
[REDACTED]

\_\_\_\_\_  
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Biostatistics Lead  
Ablynx



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**1. Introduction**

Study ALX0171-C201 is a Phase 2b multicentre study in infants and young children aged 28 days to 2 years (with a gestational age of  $\geq 33$  weeks) who are hospitalized for RSV LRTI. The design of the study is described in Section 3.1. For this dose-ranging clinical trial, sequential dose escalation is foreseen, followed by a parallel part.

In order to explore the relationship between administered ALX-0171 and serum concentration levels, an exploratory analysis of dose and drug concentration in plasma will be performed by an independent statistician from the CRO (see section 3 for blinding information) after the sequential part of the study (i.e., after Safety Cohort 3). Based on the results, an assessment will be provided to the sponsor’s Executive Committee concerning the relationship between dose and plasma concentration levels.

The purpose of this document is to describe the different aspects of this exploratory analysis.

**2. BACKGROUND INFORMATION ON STUDY**

**2.1. Study Objectives**

**2.1.1. Primary Objective**

The primary objective as defined in the protocol is to evaluate the anti-viral effect and safety of different doses of inhaled ALX-0171 in subjects hospitalized for RSV LRTI.

**2.1.2. Secondary Objectives**

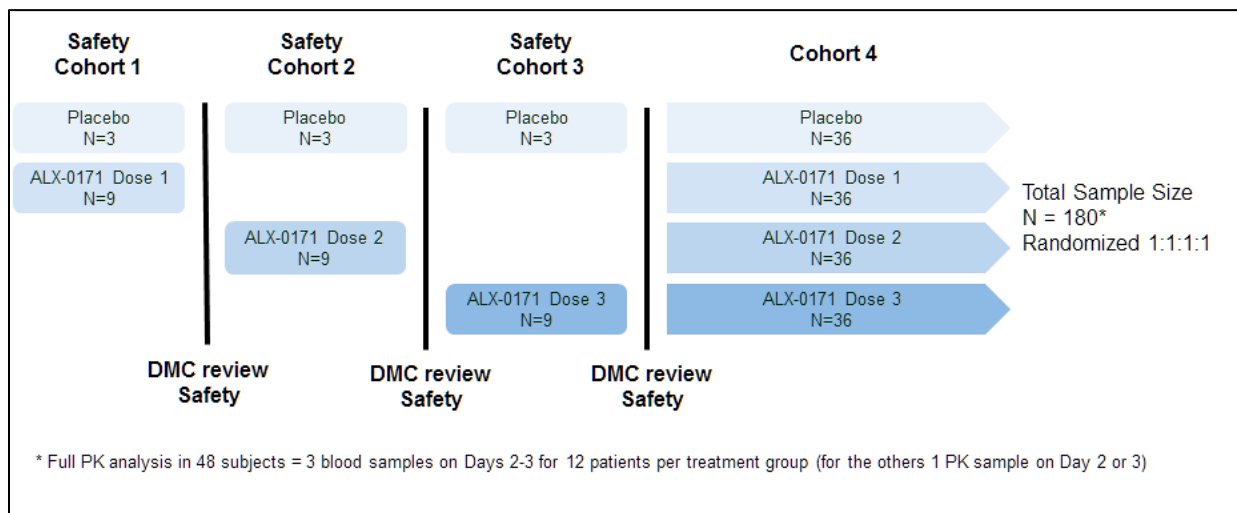
The secondary objectives as defined in the protocol are:

- To evaluate the clinical activity, PK properties, pharmacodynamic (PD) effect and immunogenicity of different doses of inhaled ALX-0171

**2.2. Study Design**

This is a randomized, double-blind, placebo-controlled, international, multicenter dose-ranging study. The study design is shown in Figure 1.

The planned enrollment in this study is approximately 180 infants and young children hospitalized for RSV LRTI. Subjects will be randomly assigned to one of three dose levels of ALX-0171 or placebo (N=45 per treatment group), yielding an overall allocation ratio of 3:1 active to placebo.



**Figure 2: Overview of study design**

The three dose levels planned to be evaluated in this study are:

- Dose 1: target dose of 3.0 mg/kg
- Dose 2: target dose of 6.0 mg/kg
- Dose 3: target dose of 9.0 mg/kg

Study drug is administered once daily for 3 consecutive days.

The study consists of a sequential part (first 36 subjects) followed by a parallel part. Further details on the dose escalation and stopping criteria are available in section 3.1.1 of the protocol and section 2.2 of the IDMC charter for the study.

Regular PK assessments (one sample) will be performed on Day 2 or Day 3, at any time between 0.5 hours post second dose and start of the third dose.

Additionally 48 subjects will undergo more extensive PK analysis (3 PK samples per subject instead of the 1 sample) at following timepoints:

1. pre dose of the second dose,
2. at any time between 0.5 hours and 3 hours post second dose
3. at any time between 3 hours and 6 hours post second dose (and at least 1 hour apart from the previous sampling).

### 3. BLINDING

The reporting biostatistician will have access to unblinded study data to be able to perform the required analysis. In case the reporting biostatistician feels this is needed, a second statistician can be unblinded to assist in the analysis and this fact will be reported to the sponsor. The analysis will be conducted on a protected server location with documented access to ensure only the authorized statistician(s) will have access. Since both Reporting Statistician as optional second unblinded Statistician will be unblinded, they will not be involved in any other study activities performed (IDMC, Main Study Analysis etc.) within the same study.

As the assessment provided will only contain general information (see section 6) and no actual analysis results, the sponsor will remain blinded during the course of this analysis. The assessment should be provided to the Executive Committee of Ablynx. The Ablynx team involved in the study will not be informed of the assessment

Additional supporting people at CRO site (e.g. Biostatistical Coordinator etc.) will remain blinded.

#### 4. ROLES AND RESPONSABILITIES

##### 4.1. Sponsor

The Sponsor is responsible for the oversight and conduct of the clinical trial. The sponsor will keep the reporting statistician informed on recruitment and planning of the actual concentration assessment analysis. The Sponsor will also ensure that the reporting statistician is provided with the requested data as described in this plan. Some of these responsibilities may be delegated to CRO's engaged by the Sponsor. As such the unblinded study data will be provided by ██████ Secure Data Office department to the unblinded statistician.

##### 4.2. Data Management

After the last subject in the last safety cohort (i.e. Cohort 3) has completed the treatment period, the PK data will be provided to the reporting statistician by ██████ Secure Data Office. The reporting statistician will also receive unblinded treatment codes from the IWRS system. No formal interim lock of the database will be performed for this analysis.

##### 4.3. Reporting Statistician

The reporting statistician is responsible for preparing the dose concentration assessment analysis and formulating an assessment according to section 5 and 6. The reporting statistician will remain independent from the study team at all times. It is expected that the assessment to the Executive Committee of Ablynx will be available within 10 to 15 working days after receiving the PK data.

#### 5. General Approach for Statistical Analysis

All concentrations are scheduled between the second and third intake.

BQL values will be considered missing in the analysis

##### 5.1. Data used in the analysis

In order to be able to assess the dose concentration relationship the unblinded statistician at the CRO will have access to general demographic, exposure and PK concentration data but will not be able to access additional safety/efficacy information from the database (AE, ECG, LAB etc.)

##### 5.2. Descriptive exploration of the data

The primary interest will be whether there are differences in concentration between the dose groups, but imbalances in the other variables will also be looked at as these may also explain concentration differences between dose groups. Therefore, the following summary will be provided:

Table 1: Descriptive Statistics of all relevant variables by dose group

- Descriptive summary of
  - Age, Weight
  - ALX-0171 concentration, Time of PK sampling relative to the first and second dose, Time of second dose relative to first dose
- Frequency tabulation of rich sampling (Yes/No), gender.

##### 5.3. Graphical exploration of the data

Figure 1: Graphical presentation of concentration vs time since first dose

Figure 2: Graphical presentation of concentration vs time since second dose

The individual concentrations will be shown as scatters and a smoothed line will be drawn per dose group. These graphs will allow a visual comparison of concentrations from different dose groups with a comparable time since first / second dose.

As a MOCK for Figure 1 and 2:

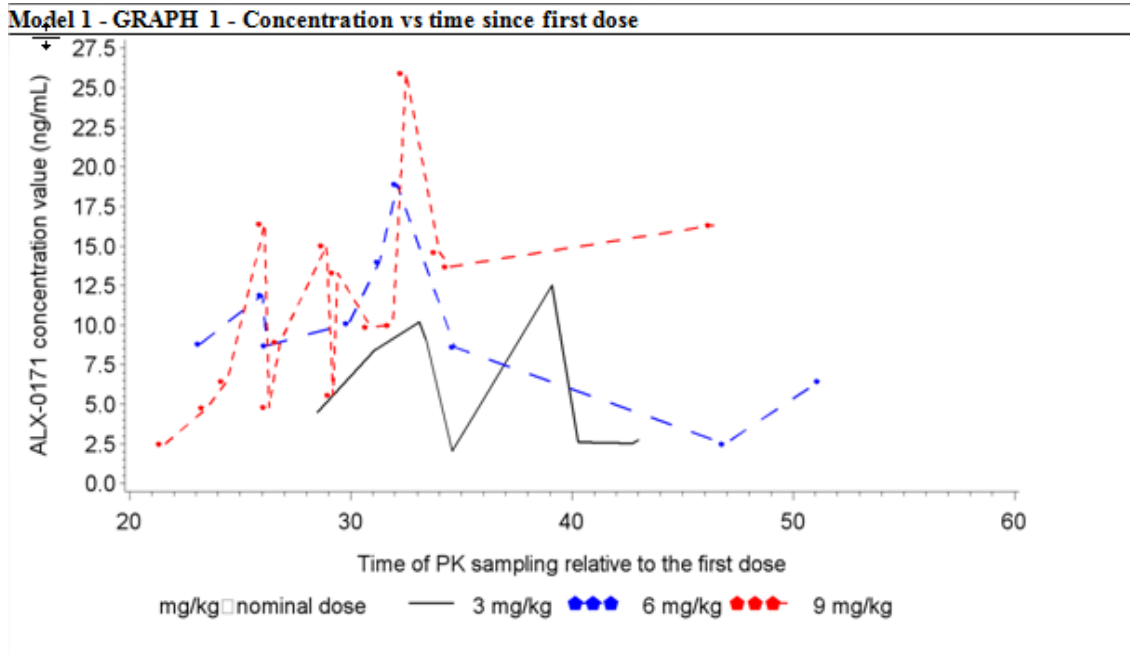


Figure 3: Graphical presentation of rich concentrations vs time since first dose

Figure 4: Graphical presentation of rich concentrations vs time since second dose

For these graphs, the concentrations from a single subject will be connected and each dose group will be shown in a separate color.

As a MOCK for figure 3 and 4:

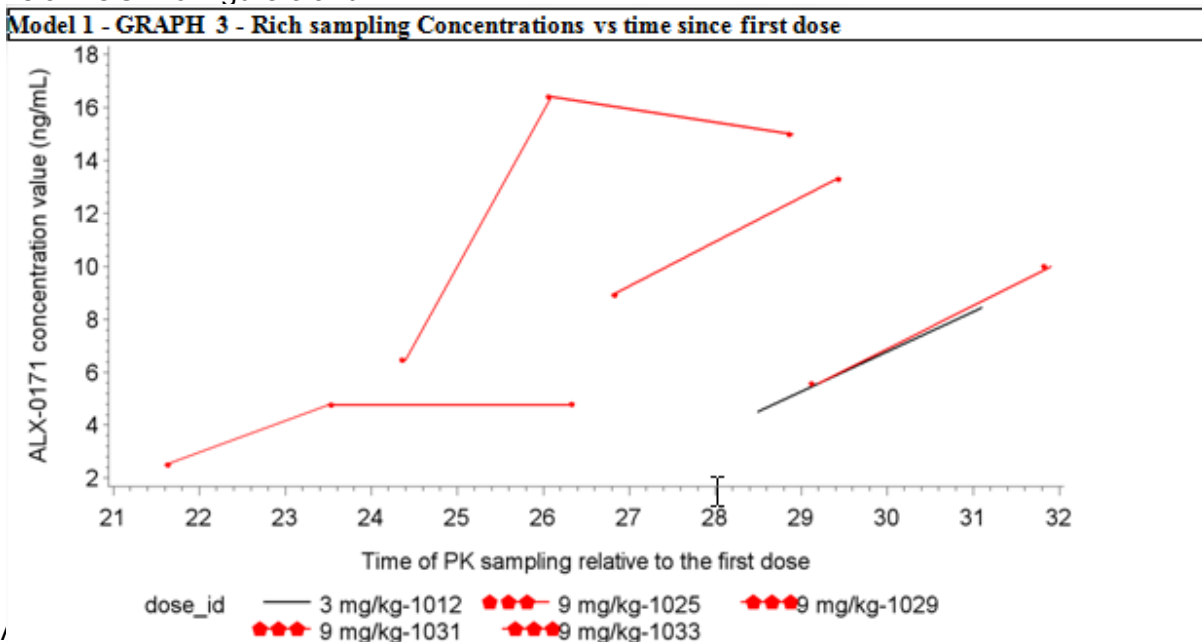
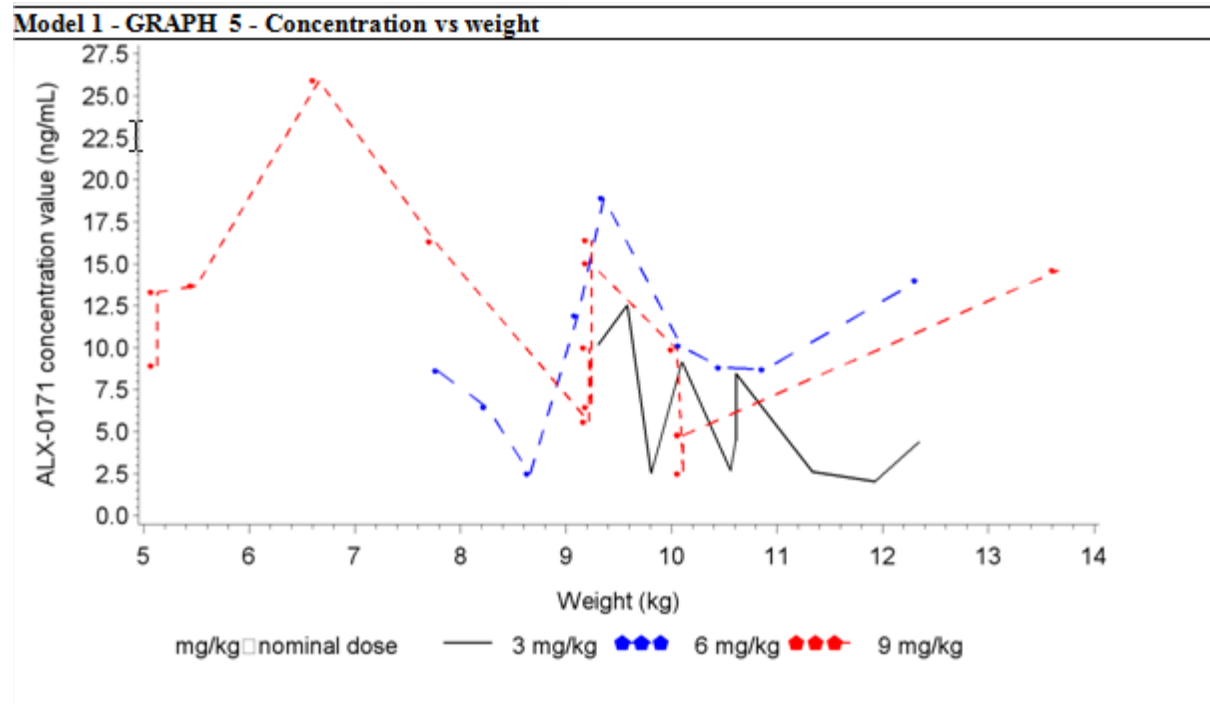


Figure 5: Graphical presentation of weight vs concentration

For this graph, the concentrations from a single dose group will be connected and weight is on the X-axis.

As a MOCK for Figure 5:



**5.4. Regression model**

Table 2: Regression on concentration

A regression analysis will be performed on concentration including time since first and second dose, weight and age as covariates; and dose group and sex as factors.

This table will present the LS-Means (and 95%CI) of the dose groups and Type III statistics for all variables in the model.

The model diagnostics will be looked at.

**5.5. Observation**

A conclusion as described in Section 6 will be drawn after close inspection and taking into account all information from this set of tables and figures. Dependent on the availability (eg. number of subjects with extensive PK sampling, distribution) and nature of the data (eg. outliers), other analyses may be performed such as comparison of concentrations matched on bins of time since first/second dose or non-parametric analysis.

**5.6. Software**

SAS version 9.2 will be used for programming.

**6. FORMAT OF ASSESSMENT**

The assessment that will be provided to the sponsor's Executive Committee will only contain general information on the relationship between ALX0171 dose groups and plasma concentrations in one of the following formats:

Based on the exploratory analysis of the data:

- 7. There is an increase in concentration with increasing dose
- 8. There is no increase in concentration with increasing dose
- 9. The relationship between dose and plasma concentration cannot be assessed

No detailed analysis results or statistical inferences will be provided to the sponsor at this time. The assessment and any follow up communication will be documented and filed in the study binder. This implies that no subject related data will be provided to the sponsor to ensure the blind is maintained.

**19.3 Appendix C: Major Protocol deviation criteria with potential impact on primary efficacy (Subset of the full trial Protocol deviations criteria list)**

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)
1.	The subject is younger than 28 days of age or 2 years or older (>= 24.00 months) of age at the time of signing Informed consent form (ICF), but the subject was randomized. - or - The subject's gestational age at birth is less than 33 weeks, but the subject was randomized.	Selection criteria not met	Inclusion criterion 1 not met: Subject is <specify age in months/days> old at date of informed consent. - or - Inclusion criterion 1 not met: Subject's gestational age is <specify age> weeks at birth.
2.	The subject's weight at screening is less than 3.0 kg or 15.0 kg or more, but the subject was randomized.	Selection criteria not met	Inclusion criterion 2 not met: Subject's weight at screening is not between 3.0 and 15.0 kg.
3.	Apart from a clinical diagnosis with RSV LRTI including typical RSV symptoms, the subject is not healthy at screening, but the subject was randomized.	Selection criteria not met	Inclusion criterion 3 not met: Subject is not healthy, apart from the clinical RSV diagnosis.
4.	For subjects enrolled under Protocol v2.0: The subject does not have a positive RSV diagnostic test, but the subject was randomized.  For subjects enrolled under Protocol v3.0: The subject does not have a positive RSV diagnostic test at screening, but the subject was randomized.	Selection criteria not met	Inclusion criterion 4 not met: Subject does not have a positive RSV diagnostic test.  Inclusion criterion 4 not met: Subject does not have a positive RSV diagnostic test at screening.
5.	The subject is not expected to stay in the hospital for at least 24 hours (according to the Investigator's judgement at screening), but the subject was randomized.	Selection criteria not met	Inclusion criterion 5 not met: Subject is not expected to stay in hospital for at least 24 hours.
6.	RSV symptoms have appeared more than 4 days before screening date, but the subject was randomized. - or - For subjects enrolled under Protocol v2.0: Since the start of the RSV infection, the RSV symptoms have improved at screening, but subject was randomized.  For subjects enrolled under Protocol v3.0: Since the start of the RSV infection, the RSV symptoms have improved at screening or randomization, but subject was randomized.	Selection criteria not met	Inclusion criterion 6 not met: RSV symptoms appeared more than 4 days prior to screening - or - Inclusion criterion 6 not met: RSV symptoms have improved at screening.  Inclusion criterion 6 not met: RSV symptoms have improved at screening or randomization.
7.	For subjects enrolled under Protocol v2.0: Subject does not fulfill at least two of the three RSV disease severity criteria: - Inadequate oral feeding that requires feeding support - Inadequate oxygen saturation - Signs of respiratory distress, but subject was randomized.  For subjects enrolled under Protocol v3.0: Subject does not fulfill at least two of the three RSV disease severity criteria at screening or randomization: - Inadequate oral feeding that requires feeding support - Inadequate oxygen saturation - Signs of respiratory distress, but subject was randomized.	Selection criteria not met	Inclusion criterion 7 not met: Subject does not fulfill at least two of the RSV disease severity criteria (<specify criteria not fulfilled>).  Inclusion criterion 7 not met: Subject does not fulfill at least two of the RSV disease severity criteria at screening or randomization (<specify criteria not fulfilled>).
8.	Subject does not have a normal psychomotor development, but subject was randomized.	Selection criteria not met	Inclusion criterion 8 not met: Subject does not have a normal psychomotor development.



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Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)
11.	The subject has 1 or more significant comorbidity(ies), but subject was randomized.	Selection criteria not met	Exclusion criterion 1 met: Subject is known to have significant comorbidity(ies) (<specify comorbidity>).
12.	The subject is known to be human immunodeficiency virus (HIV)-positive, but subject was randomized. - or - The subject is < 6 months of age and the mother is known to be HIV-positive, but subject was randomized.	Selection criteria not met	Exclusion criterion 2 met: Subject is known to be HIV-positive. - or - Exclusion criterion 2 met: Subject is less than 6 months old and subject's mother is known to be HIV-positive.
13.	The HIV status of the subject is unknown at screening. The subject is HIV-positive as confirmed by a local laboratory test performed at screening, but subject is randomized. - or - The subject is < 6 months of age and the mother is HIV-positive as confirmed by a local laboratory test performed at screening, but subject is randomized.  <i>Only applicable for subjects participating under: - CTP 1.0 - South Africa v1.0 dd. 04/AUG/2016</i>	Selection criteria not met	Exclusion criterion 2 met: Subject is HIV-positive, as confirmed by a local lab test at screening. - or - Exclusion criterion 2 met: Subject is less than 6 months old and subject's mother is HIV-positive as confirmed by a local lab test at screening.
15.	The subject is known to be immunocompromised, but subject was randomized.	Selection criteria not met	Exclusion criterion 3 met: Subject is known to be immunocompromised.
16.	The subject has or is suspected to have an active clinically relevant concurrent infection, but subject was randomized.	Selection criteria not met	Exclusion criterion 4 met: Subject has an active clinically relevant concurrent infection (<specify disease>).
17.	The subject has significant oral and/or maxillofacial malformations which prevent proper positioning of the face mask, but subject was randomized.	Selection criteria not met	Exclusion criterion 5 met: Subject has significant oral and/or maxillofacial malformations.
18.	The subject has received invasive mechanical ventilation or non-invasive respiratory support in the 4 weeks prior to screening, but subject was randomized.	Selection criteria not met	Exclusion criterion 6 met: Subject has received invasive mechanical or non-invasive respiratory support in the 4 weeks prior to screening.
19.	During the current hospital admission, the subject is initially hospitalized in ICU setting and/or the subject received invasive mechanical ventilation, non-invasive respiratory support, but subject was randomized.	Selection criteria not met	Exclusion criterion 7 met: Subject was initially hospitalized in ICU and/or subject received invasive mechanical ventilation, non-invasive respiratory support
20.	The subject is critically ill, but subject was randomized. - or - The subject is expected to require invasive mechanical ventilation, non-invasive respiratory support or High Flow oxygen therapy (HFOT) at levels not enabling nebulization therapy, but subject was randomized.	Selection criteria not met	Exclusion criterion 8 met: Subject was critically ill. - or - Exclusion criterion 8 met: Subject is expected to require (non-) invasive ventilation at levels not enabling nebulization therapy.
21.	The subject has received 1 or more doses of palivizumab or treatment or prophylaxis with any RSV antiviral compound at any time prior to screening, but subject was randomized. - or - The subject's mother has been vaccinated against RSV prior to screening, but subject was randomized.	Selection criteria not met	Exclusion criterion 9 met: Subject has received treatment or prophylaxis with any RSV antiviral compound at any time prior to screening. - or - Exclusion criterion 9 met: Subject's mother has been vaccinated against RSV prior to screening.
22.	The subject is required to continue or start systemic corticosteroid therapy, but subject was randomized.	Selection criteria not met	Exclusion criterion 10 met: Subject is required to continue or start systemic corticosteroid therapy.



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Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)
24.	The subject is currently participating in any other study with investigational drug, but subject was randomized. - or - The subject has received an investigational drug within 4 weeks or 5 half-lives of the concerned drug (whichever is longer) prior to screening, but subject was randomized.	Selection criteria not met	Exclusion criterion 12 met: Subject is participating in another study with investigational drug. -or- Exclusion criterion 12 met: Subject has received an investigational drug within 4 weeks or 5 half-lives of the concerned drug prior to screening.
25.	The subject was previously enrolled in a clinical study of ALX-0171 (including ALX0171-C201), but subject was randomized.	Selection criteria not met	Exclusion criterion 13 met: Subject was previously enrolled in a clinical study of ALX-0171.
38.	The first of the 2 serial nebulizations is started successfully but needs to be interrupted, and nebulization could not be completed within 2 hours after nebulizer filling of this nebulization. - or - The second of the 2 serial nebulizations could not be completed within 2 hours after nebulizer filling of this nebulization.	Treatment non-compliance	The <specify type of nebulization> at <specify visit> is interrupted and could not be completed within 2 hours (<specify exact timing>) after filling.
39.	The first of the 2 serial nebulizations was not initiated successfully. - or - The second of the 2 serial nebulizations was not initiated successfully.	Treatment non-compliance	The <specify type of nebulization> at <specify visit> was not initiated successfully.
40.	The first of the 2 serial nebulizations was initiated successfully, but administration was not fully done. - or - The second of the 2 serial nebulizations was initiated successfully, but administration was not fully done.	Treatment non-compliance	The <specify type of nebulization> at <specify visit> could not be completed successfully.
41.	Administration of both serial nebulizations exceeded the maximum time window of 4 hours.	Treatment non-compliance	Study drug administration at <specify visit> exceeded the maximum time window of 4 hours (<specify exact timing>).
43.	Study drugs with rejected IMP were administered to the subject: deviations to the study drug storage conditions occurred, which were not approved by the Sponsor.	Treatment non-compliance	Dosing with rejected IMP: deviations to the study drug storage conditions occurred when study drug was administered to subject (<specify type of nebulization> at <specify visit>).
44.	The dose of study drug was (temporarily) not according to the weight category range, as per protocol.	Treatment non-compliance	A wrong dose (<specify dose>) of study drug was taken on <specify type of nebulization> at <specify visit>.
47.	The subject received study drug administration(s) outside the 24-hour intervals (+/- 4 hours) relative to the first dose (i.e. outside the 24h (+/- 4h) window on Day 2 relative to start of first nebulization on Day 1, or outside the 48h (+/- 4h) window on Day 3 relative to start of first nebulization on Day 1).	Treatment non-compliance	Study drug dosing window deviation: administration outside the 24-hours interval (<specify hours> between <specify type of nebulization> at <specify visit> and first nebulization at Day 1).
48.	The nebulizer is used during study drug administration with a fixed air/O2 flow rate different from 2 L/min.	Treatment non-compliance	Fixed air/O2 flow rate during study drug administration is different from 2 L/min (<specify type of nebulization> at <specify visit>).

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Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)
49.	During study drug administration, the face mask is not always (less than 75% of the time) in contact with the face of the subject.	Treatment non-compliance	Face mask is not always in contact with the face of the subject (<specify type of nebulization> at <specify visit>).
50.	The subject has a missed dose without having fulfilled the study drug discontinuation criteria or without having discontinued the study.	Treatment non-compliance	Subject has a missed dose of study drug at <specify visit>.
51.	The study drug was administered by a route other than inhalation.	Treatment non-compliance	Administration of study drug (<specify type of nebulization> at <specify visit>) by a route other than inhalation.
52.	The device number(s) or medication kit number dispensed to the subject was not the same as the number assigned by IWRS.	Treatment non-compliance	<Base unit serial / Inhalation set / Medication kit> number dispensed to subject was not the same as the number assigned by IWRS for <specify type of nebulization> at <specify visit>.
53.	The subject was administered an expired study drug.	Treatment non-compliance	Subject was administered expired study drug (<specify type of nebulization> at <specify visit>).
54.	The subject received oxygen supplementation through a nasal cannula, face mask or headbox, but nasal cannula, face mask or headbox was not removed immediately before study drug administration.	Treatment non-compliance	Nasal cannula, face mask or headbox was not removed before study drug administration (<specify type of nebulization> at <specify visit>).
55.	The subject started treatment with one of the forbidden medications, as defined per protocol, during the study up to the Follow-up visit.	Prohibited concomitant medication	Subject started treatment with forbidden medication during the study up to the Follow-up visit (<specify term, dose, unit, frequency, start and end date, reason administered>).
56.	The subject received hypertonic saline within 4 hours before the start or 4 hours after the end of study drug administration.	Prohibited concomitant medication	Subject received hypertonic saline within 4 hours before start (<specify exact timing>) or 4 hours after end (<specify exact timing>) of study drug administration at <specify visit>.
57.	A planned collection of a nasal mid-turbinate swab was not performed. This should only lead to exclusion from PP population if the missing nasal swab occurred before 2 consecutive BQL values.	Efficacy assessment deviation	Nasal mid-turbinate swab was not collected on <specify timepoint> at <specify visit>.
58.	A planned nasal mid-turbinate swab is taken out of time window. This should only lead to exclusion from PP population if the nasal swab out of time window occurred before 2 consecutive BQL values.	Efficacy assessment deviation	The nasal mid-turbinate swab on <specify timepoint> at <specify visit> was taken out of time window (<specify exact timing>).
70.	The subject is re-hospitalized or consults the Investigator for a respiratory condition after hospital discharge up to EOS visit. At this unscheduled visit, the nasal mid-turbinate swab was not collected. This should only lead to exclusion from PP population if the nasal swab not collected occurred before 2 consecutive BQL values.	Efficacy assessment deviation	The subject is re-hospitalized or consults the Investigator for a respiratory condition, but <specify assessment>
72.	A nasal mid-turbinate swab was collected using an expired kit and/or expired medium. This should only	Efficacy assessment deviation	The nasal mid-turbinate swab on <specify timepoint> at <specify visit> was collected

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Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)
	lead to exclusion from PP population if the nasal swab was collected before 2 consecutive BQL values.		using an expired kit and/or medium.
75.	A nasal mid-turbinate swab was collected, but a deviation in the sample storage conditions occurred. This should only lead to exclusion from PP population if the missing nasal swab occurred before 2 consecutive BQL values.	Efficacy assessment deviation	Deviation occurred in sample storage condition of nasal mid-turbinate swab collected on <specify timepoint> at <specify visit>.

**19.4 Appendix D: List of viral screening tests:**

- Influenza A
- Influenza A H1N1
- Influenza B
- Coronavirus NL63
- Coronavirus 229E
- Coronavirus OC43
- Coronavirus HKU1
- Human Parainfluenza Virus 1
- Human Parainfluenza Virus 2
- Human Parainfluenza Virus 3
- Human Parainfluenza Virus 4
- Human Metapneumovirus A and B
- Human rhinovirus
- Human Respiratory Syncytial Viruses A and B
- Adenovirus
- Enterovirus
- Human Parechovirus
- Human Bocavirus
- Mycoplasma Pneumoniae