



# CLINICAL STUDY PROTOCOL

## ALX0171-C203

**A randomized, double-blind, multicenter, multiple-dose study of ALX-0171 versus placebo along with standard of care in Japanese infants and young children hospitalized for respiratory syncytial virus lower respiratory tract infection**

<b>Short Title:</b>	Evaluation of ALX-0171 in Japanese children hospitalized for RSV lower respiratory tract infection
<b>Investigational Product:</b>	ALX-0171 nebulizer solution
<b>Sponsor Protocol Code:</b>	ALX0171-C203
<b>Sponsor:</b>	Ablynx NV Technologiepark 21 9052 Zwijnaarde, Belgium
<b>Phase of Development:</b>	Phase 2
<b>Indication:</b>	Treatment of RSV lower respiratory tract infection
<b>Study Center:</b>	Multicenter
<b>Protocol Date:</b>	13 November 2017
<b>Protocol Version:</b>	Version 3.0
<b>Protocol Status:</b>	Final

This study will be performed in compliance with the Clinical Study Protocol, the principles of Japan - and International Council on Harmonization - Good Clinical Practice (ICH-GCP), and the applicable regulatory requirement(s).

## **CONFIDENTIALITY STATEMENT**

The information contained in this document, especially unpublished data, is the property of Ablynx NV (or under its control), and therefore provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your study staff, and applicable Institutional Review Board (IRB). It is understood that this information will not be disclosed to others without written authorization from Ablynx NV, except to the extent necessary to obtain informed consent from the parent(s)/legal guardian(s) of the persons to whom the study drug may be administered.

# APPROVAL OF CLINICAL STUDY PROTOCOL

The Sponsor and the Investigator(s) agree to conduct the study as outlined in this Clinical Study Protocol. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator(s), and must be documented in writing.

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**Sponsor:**

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Name: [REDACTED]

Function: Senior Medical Director

Signature – Date: *See signature page at the end of the document*

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**Investigator:**

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I have read Clinical Study Protocol ALX0171-C203 and agree to personally conduct or supervise the clinical study in accordance with this Clinical Study Protocol, with the terms of the clinical trial agreement and with any other study procedures and documents provided by Ablynx NV.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

I confirm that the study team and I will not implement any deviations from this Clinical Study Protocol without agreement of Ablynx NV, except where necessary to eliminate an immediate hazard to the patients.

I confirm that I am thoroughly familiar with the appropriate use of the study drug, as described in this Clinical Study Protocol and any other information provided by Ablynx NV.

I confirm that I am aware of and will comply with Japan- and ICH-GCP and all applicable national and regional regulations/guidelines.

Hence, I agree to supply Ablynx NV with any necessary information regarding the ownership interest and financial ties, to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study, and that Ablynx NV may disclose any available information about such ownership interest and financial ties to regulatory authorities.

Principal Investigator Name:

Site details/Address:

Signature – Date:

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## **SERIOUS ADVERSE EVENT CONTACT INFORMATION**

Contact details of the Sponsor and third parties are available in the "Investigator Site File".

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## LIST OF ABBREVIATIONS AND DEFINITIONS

ADA	Anti-drug antibodies
AE	Adverse event
AR	Adverse reaction
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BID	Twice a day (bis in die)
BQL	Below the limit of quantification
CE	Conformité Européene
CL/F	Apparent clearance
C <sub>max</sub>	peak plasma concentration
cPAP	Continuous positive airway pressure
CRO	Contract research organization
CSR	Clinical Study Report
DAP	Data analysis plan
DIN	Deutsches Institut für Normung (German Institute For Standardization)
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
F protein	Fusion protein
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HFOT	High-flow oxygen therapy
HIV	Human immunodeficiency virus
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
ID	Identification
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IWRS/IVRS	Interactive web/voice response system
KL-6	Krebs von den Lungen-6
LBA	Ligand binding assay

Legal guardian(s)	Authorized representative(s) for the subject, according to local legislation
LRTI	Lower respiratory tract infection
LSLV	Last visit of the last subject
LTRA(s)	Leukotriene Receptor Antagonist(s)
mAb	Monoclonal antibody
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
mITT	Modified Intent-to-treat
mRNA	Messenger ribonucleic acid
N	Number of subjects
NAb	Neutralizing anti-drug antibodies
PBPK	physiologically based pharmacokinetic (model)
pCO <sub>2</sub>	partial pressure of carbon dioxide
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PFU	Plaque forming unit
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
Pre-Ab	Pre-existing antibodies
QD	once a day (quaque die)
qPCR	quantitative polymerase chain reaction
RACS	Respiratory Assessment Change Score
RDAI	Respiratory Distress Assessment Instrument
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-qPCR	real-time (quantitative) polymerase chain reaction
SAE	Serious adverse event
SAINT	Sophia anatomical infant nose-throat
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SpO <sub>2</sub>	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reactions
TE	Treatment-emergent
TE ADA	Treatment-emergent anti-drug antibodies
TEAE(s)	Treatment-emergent adverse event(s)
VAS	Visual Analogue Scale
WHO	World Health Organization

## CHANGES COMPARED TO PREVIOUS VERSION(S)

Protocol version 1.0 was not submitted for approval to any Regulatory Authority or Institutional Review Board (IRB)/Ethics Committee. Version 1.0 was provided to potential Investigators and clinical sites for initial review and feasibility evaluation only. Minor corrections were made in protocol version 2.0.

**Global Version 3.0 (dated 13 November 2017) compared to Global Version 2.0 (dated 5 September 2017). This amendment is considered substantial as new exclusion criteria and screening assessments were added to the study following the request of the Pharmaceuticals and Medical Device Agency (PMDA) Japan.**

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents was updated. The section "Changes Compared to Previous Version(s)" was updated with the changes of the current amendment, use of abbreviations and the abbreviations list had minor updates stemming from the amendment changes.

Section affected	Change/ Rationale
Schedule of Assessments; Section 3.6.1.2.	The Schedule of Assessments underwent the following change: 12-lead ECG was added as an additional screening assessment. As such this was also added to assessments performed at screening.
Synopsis, Exclusion criteria Section 3.2.2.	There was an exclusion criterion added to perform and assess a 12-lead ECG at screening for any clinically significant abnormalities that would not allow the subject to be included according to the Investigators' judgement. An additional criterion was added to exclude subjects considered ineligible for participating in the trial for safety reasons or any other concerns of the Investigator.
Section 4.1.6.	Added reporting deadlines for SUSAR expedited reporting to PMDA, IRB and Investigator.

# PROTOCOL SYNOPSIS

**Protocol title**

A randomized, double-blind, multicenter, multiple-dose study of ALX-0171 versus placebo along with standard of care in Japanese infants and young children hospitalized for respiratory syncytial virus lower respiratory tract infection

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**Protocol short title**

Evaluation of ALX-0171 in Japanese children hospitalized for respiratory syncytial virus (RSV) lower respiratory tract infection

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**Investigational product**

ALX-0171 nebulizer solution

The active pharmaceutical ingredient is ALX-0171 Nanobody, a therapeutic protein directed against the fusion protein of the human RSV.

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**Sponsor Protocol Code**

ALX0171-C203

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**Sponsor**

Ablynx NV  
Technologiepark 21  
9052 Zwijnaarde, Belgium

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**Phase of Development**

Phase 2

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**Indication**

Treatment of RSV lower respiratory tract infection

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**Study centre**

Multicenter

## Objectives

- To evaluate the safety, tolerability and systemic pharmacokinetics (PK) of different doses of inhaled ALX-0171 in Japanese infants and young children hospitalized for RSV LRTI.
  - To evaluate the antiviral effect, clinical activity, immunogenicity, and pharmacodynamics (PD) of different doses of inhaled ALX-0171 in Japanese infants and young children hospitalized for RSV LRTI.
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## Study Design

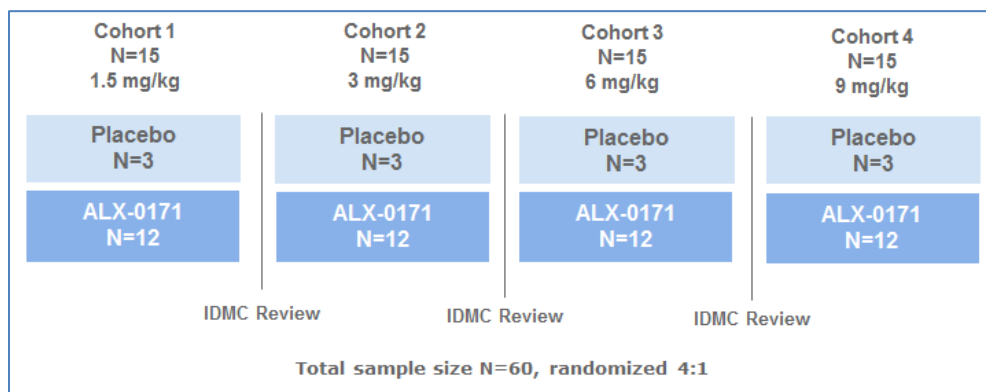
This is a randomized, double-blind, multicenter, multiple-dose study of ALX-0171 versus placebo along with standard of care. The study population will consist of 60 Japanese infants and young children aged 28 days to <2 years with a gestational age  $\geq$  33 weeks who are hospitalized for and diagnosed with RSV LRTI. Four dose levels are planned to be evaluated in four consecutive cohorts:

- Dose level 1: target dose of 1.5 mg/kg
- Dose level 2: target dose of 3.0 mg/kg
- Dose level 3: target dose of 6.0 mg/kg
- Dose level 4: target dose of 9.0 mg/kg

Each dose level has the potential to be of benefit to the subjects. The study will provide information on safety, tolerability, PK, antiviral effect, clinical activity, immunogenicity, and PD across a relevant range, and is intended to support selection of an optimal dose of ALX-0171 for further clinical development, taking ethnicity into consideration.

- The starting dose level is the same dose level evaluated in the first-in-infant study, ALX0171-C104, which was conducted outside of Japan. In total, 53 infants and young children hospitalized for RSV LRTI were enrolled. The results of study ALX0171-C104 indicated that this dose was well tolerated in all age groups (28 days to 24 months). Reductions in nasal viral load (obtained from nasal swabs) were noted, confirming that ALX-0171 exhibits antiviral activity.
- Dose levels 2, 3 and 4 are the same as those currently being evaluated in the Phase 2b dose-ranging study ALX0171-C201, which is being conducted outside of Japan (N=180 infants and young children hospitalized for RSV LRTI).

Each cohort will consist of 15 subjects enrolled and randomly assigned to receive ALX-0171 or placebo, in an allocation ratio of 4:1 (N=12 active versus N=3 placebo per dose level). Study drug will be administered once daily for 3 consecutive days and will be given along with standard of care treatment, which will be determined by the Investigator according to institutional practice (taking into account the prohibited medications listed in section 3.3.7). The 3-day treatment period is expected to bridge the time needed for the body to mount an effective immune response.

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IDMC=Independent Data Monitoring Committee

After the last subject in a cohort has completed his/her treatment period or has discontinued study drug, an Independent Data Monitoring Committee (IDMC) consisting of an independent group of clinical experts, will review the cumulative unblinded safety data (i.e., all available data for all included subjects, including preceding cohorts) and advise the Sponsor on proceeding to the subsequent cohort (i.e., the next higher dose). The participants, objectives, and roles and responsibilities of the IDMC will be described in an IDMC Charter. Recruitment will be paused while the IDMC reviews the data of each cohort. Serious adverse event (SAE) information will be communicated to the IDMC in real time throughout the study, as per the IDMC Charter. An ad-hoc meeting can be requested by the IDMC members at any time.

In addition to the individual discontinuation criteria (see section 3.4), criteria for stopping or pausing recruitment in each cohort and criteria to stop dose escalation will apply (see section 3.1.1).

## Study Flow

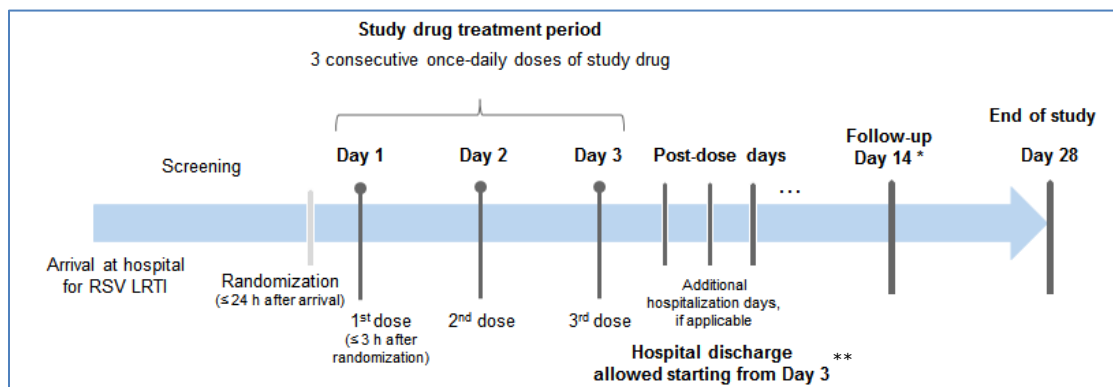
Upon signing of the Informed Consent Form by the parent or legal guardian, subjects will be screened as soon as possible after arrival at the hospital/emergency unit.

- After completion of the screening assessments and confirmation of subject's eligibility, randomization should follow as soon as possible but not longer than 24 hours after arrival at the hospital/emergency unit.
- Subjects will receive once-daily doses of study drug on 3 consecutive days. Study drug administration should start as soon as possible after randomization with a maximum time interval of 3 hours following randomization. Subsequent doses of study drug will be administered at 24-hour intervals ( $\pm 4$  hours) relative to the first dose. No pre-medication is required per protocol, but an inhaled  $\beta_2$ -agonist may be administered at the discretion of the treating Investigator.
- During the 3 treatment days, inpatient hospital stay is required.
- Discharge from the hospital can take place per protocol at the Investigator's discretion from dosing on Day 3 onwards, after all required assessments of the 5 hours ( $\pm 1$  hour)

post-dose time point have been completed and provided that the clinical response criteria have been met. Subjects who are not discharged from the hospital after completion of the treatment period will enter an in-hospital post-treatment period with assessments in the morning and evening until discharged.

- 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).
- In case a subject is re-hospitalized, or when the Investigator is consulted for a respiratory condition occurring after discharge from the hospital, an Unscheduled Visit is to be performed. In such cases, a mid-turbinate nasal swab is to be collected and a physical examination, including lung auscultation, must be performed. In addition, Unscheduled Visits may be conducted to assess or follow-up on AEs or laboratory abnormalities. In such cases, the evaluations performed are at the discretion of the Investigator.
- For subjects prematurely withdrawn from the study, a Withdrawal visit is to be performed on the day of withdrawal.
- Subjects who discontinue study drug (for any reason) but remain hospitalized will enter the in-hospital post-treatment period and will be followed up twice daily (in the morning and the evening) until they are discharged from the hospital. They should also attend the FU and EOS visit.

After the end of the subject's participation in the study, each subject is to be treated according to standard clinical practice.



\*Or withdrawal visit at earlier time point in case of withdrawal

\*\*Hospital discharge is allowed from Day 3 once all post-dose assessments have been completed and clinical response criteria have been met.

## Study Duration

- The overall study duration is expected to be approximately 12 months.
- The planned study duration for each subject is approximately 28 days.
- The maximum study drug treatment duration for each subject is 3 days.
- The completion of the study is defined as the last visit of the last subject (LSLV) participating in the study.



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## Study Population

Japanese infants and young children aged 28 days to <2 years with a gestational age  $\geq 33$  weeks, hospitalized for and diagnosed with RSV LRTI (but otherwise healthy).

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## Number of Subjects

A total of 60 subjects will be randomized and treated in the study.

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## Inclusion Criteria

A subject will be eligible for study participation if he/she meets all of the following criteria at screening and randomization, unless specified otherwise.

1. Subject is a Japanese male or female infant or young child aged 28 days to <2 years with gestational age  $\geq 33$  weeks at screening.
2. Subject is of Japanese descent, i.e., born in Japan to Japanese parents and has Japanese maternal and paternal grandparents.
3. Subject weighs between  $\geq 3.0$  kg and <15.0 kg at screening.
4. Subject is otherwise healthy, but is hospitalized for and clinically diagnosed with RSV LRTI (bronchiolitis or broncho-pneumonia), i.e., showing typical clinical signs and symptoms such as tachypnea, wheezing, cough, crackles, use of accessory muscles and/or nasal flaring.
5. Subject has a positive RSV diagnostic test within 4 days of screening.\*
6. Subject is expected to have to stay in the hospital for at least 24 hours (according to the Investigator's judgment at screening).
7. Symptoms likely related to RSV infection (i.e., the symptoms present need to be probably linked to the current RSV infection according to Investigator's judgment) have appeared within 4 days of screening and are not yet improving at screening and randomization.
8. Subject fulfils at least two of the following RSV disease severity criteria at screening and randomization:
  - Inadequate oral feeding that requires feeding support (i.e., nasogastric tube or intravenous [i.v.] line),
  - Inadequate oxygen saturation defined as:
    - Oxygen saturation ( $\text{SpO}_2$ ) < 95% on room air or
    - Requiring oxygen supplementation to maintain adequate oxygen saturation with documented pre-supplementation value < 95%
  - Signs of respiratory distress defined as:
    - Respiratory rate  $\geq 50$  breaths per minute in infants up to 12 months of age, and  $\geq 40$  breaths per minute in children above 12 months and/ or
    - Moderate or marked respiratory muscle retractions

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\* RSV infection will be confirmed either according to routine site practice (PCR, immunofluorescence or diagnostic quick test), or using a Sponsor-provided commercial kit.

9. Subject has normal psychomotor development.
10. Parent(s)/legal guardian(s) provide written informed consent in accordance with locally approved consent process at screening.
11. The parent(s)/legal guardian(s) are able and willing to comply with the study protocol procedures.

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### **Exclusion Criteria**

Subjects meeting any of the following criteria at screening or randomization will not be eligible for study participation.

1. Subject is known to have significant comorbidities including:
  - Genetic disorders (e.g., trisomy 21, cystic fibrosis),
  - Hemodynamically significant congenital heart disease (e.g., needing corrective therapy or inotropic support),
  - Bronchopulmonary dysplasia,
  - Any hereditary or acquired metabolic (bone) diseases,
  - Hematologic or other malignancy.
2. Subject is known to be human immunodeficiency virus (HIV)-positive. If the subject is < 6 months of age, known HIV-positivity of the mother is also exclusionary.
3. Subject is known to be immunocompromised.
4. Subject has or is suspected to have an active, clinically relevant concurrent infection (e.g., bacterial pneumonia, urinary tract infection). Concurrent acute otitis media is not exclusionary.
5. Subject has significant oral and/or maxillofacial malformations which would prevent proper positioning of the face mask.
6. Subject received invasive mechanical ventilation or non-invasive respiratory support (i.e., continuous or bilevel positive airway pressure) in the 4 weeks prior to screening.
7. During the current admission, subject is initially hospitalized in an intensive care unit (ICU) setting and/or received invasive mechanical ventilation or non-invasive respiratory support (i.e., continuous or bilevel positive airway pressure).
8. Subject is critically ill and/or is expected to require invasive mechanical ventilation, non-invasive respiratory support (i.e., continuous or bilevel positive airway pressure), or high-flow oxygen therapy (HFOT) at levels not enabling nebulization therapy according to the Investigator's judgment. High Flow oxygen, with a maximum flow of 2 L/kg/min, is permitted under the following conditions:
  - used as Standard of Care outside ICU setting
  - can be removed for study drug administration (Note: oxygen flow at 2 L/minute can be provided through the nebulizer)
9. Subject has received 1 or more doses of palivizumab or treatment or prophylaxis with any RSV antiviral compound (e.g., ribavirin, i.v. immunoglobulin, or any investigational drug or vaccine for RSV [including subject's mother who has been vaccinated against RSV]) at any time prior to screening.

10. Subject is required to continue or start systemic corticosteroid therapy. Subject on a maintenance therapy of inhaled corticosteroids will continue this treatment at the usual dose. Topical corticosteroids for skin disorders are permitted.
11. Subject has clinically meaningful abnormalities on a 12-lead ECG, which according to the Investigator's judgement does not allow participation of the subject in the study. A 12-lead ECG performed within 4 days of screening will be acceptable. If not yet available, the 12-lead ECG should be performed at the time of screening.
12. Subject is a child in care (i.e., a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation). A child in care can thus include a child cared for by foster parents or living in a care home institution, provided that the arrangement falls within the definition above, but does not include a child who is adopted or has appointed legal representative(s).
13. Subject is currently participating in any other study with investigational drug or has received an investigational drug within 4 weeks or 5 half-lives of the concerned drug (whichever is longer) prior to screening.
14. Subject was previously enrolled in a clinical study of ALX-0171 (including the current Study ALX0171-C203).
15. Subject has a known hypersensitivity to the study drug or any excipient of the study drug.
16. Subject is considered by the Investigator to be ineligible to participate in the trial for safety reasons or any other concern.

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## **Study Medication**

### *Investigational Product*

- Name: ALX-0171 (nebulizer solution).
- Active substance: ALX-0171 Nanobody.
- Activity: ALX-0171 Nanobody specifically and potently binds to the RSV F protein, thereby inhibiting an early step in the viral replication cycle.
- Composition: [REDACTED]

### *Reference Product*

- Name: Matching placebo (nebulizer solution).
- Active substance: None.
- Composition: [REDACTED]

### *Device*

- Name: FOX-Flamingo inhalation system - CE marked.
- Main components: re-usable single-patient base unit (containing the electronics), single-use disposable inhalation set (including pediatric face mask in 2 sizes, mask adapter, vibrating mesh nebulizer with reservoir).
- Description: The FOX-Flamingo inhalation system consists of a battery-operated, hand-held device, intended for single-patient use. The device provides an aerosol with particle size suitable for the intended study population. The nebulizer is always to be used with a flow of 2 L/minute additional air or oxygen.

#### *Standard of Care*

- The treatment and care provided to each subject are determined by the Investigator (or designee) according to institutional practice (taking into account the prohibited medications listed in section 3.3.7). The recommendations on the diagnosis, management, and prevention of bronchiolitis as described by the American Academy of Pediatrics (2014) [1], may be followed in addition to institutional practice.
- Treatment may include (but is not limited to) the following:
  - Oxygen supplementation through nasal cannula, via face mask or headbox. The initiation, monitoring and weaning of oxygen supplementation will follow local practice. It should be removed for the nebulized study drug administration, during which air or oxygen flow of 2 L/minute is provided
  - Fluid/food supplementation (i.v. or via nasogastric tube, if applicable)
  - Antipyretics and/or nonsteroidal anti-inflammatory medication
  - Inhalation of hypertonic saline (but not within 4 hours before start or 4 hours after the end of study drug administration)
  - Short acting  $\beta_2$ -agonists
  - Antibiotics (in case of secondary bacterial infection)
  - Epinephrine
  - Anticholinergics

#### *Concomitant and Prohibited Medications*

Apart from those listed under the prohibited therapies, concomitant medications are permitted at the Investigator's discretion (based on medical need).

The following treatments are prohibited up to the FU visit (Day 14  $\pm$  2 days):

- Ribavirin, i.v. immunoglobulin and palivizumab
- Heliox
- Leukotriene receptor antagonists (LTRAs, i.e. montelukast) and/or sodium cromoglycate; initiation of LTRAs and/or sodium cromoglycate is not permitted; infants who are on a maintenance therapy at screening are to continue their usual dose during the study
- Exogenous surfactant
- Systemic corticosteroids; initiation of inhaled corticosteroids is not permitted; infants who are on a maintenance therapy of inhaled corticosteroids at screening are to continue their

usual dose during the study. Of note, topical corticosteroids for the treatment of skin disorders are permitted.

- Mucolytics are permitted until screening but their continuation or initiation during the study is not allowed.

## **Assessments**

Demographic and medical history data (including RSV-related signs and symptoms) will be collected at screening. Collected data will include (but are not limited to): month and year of birth, age (with indication of week), gender, race and ethnicity. Data on atopy in the family, environmental exposure to tobacco and pets, and breastfeeding will also be collected. A 12-lead ECG will be performed to assess eligibility.

The mid-turbinate nasal swab sample collected pre-dose on Day 1 will be used to test for concurrent viruses and the presence of mycoplasma at baseline. *Safety Outcome Measures*

- Treatment-emergent adverse events (TEAEs), as noted by healthcare staff and/or reported by parents/caregivers. The Investigator (or his/her designee) will review at each visit whether AEs/serious adverse events (SAEs) have occurred since the last visit.
- Heart rate, respiratory rate (measured over a 1-minute interval) and SpO<sub>2</sub>.
- Body temperature and body weight.
- Physical examination including the skin, ears/nose/throat, heart auscultation, lung auscultation, and abdomen.
- Safety lab assessments are planned two times during the study (at screening and at the FU visit) and will be performed by the local laboratory in order to allow timely availability of the results. The following clinical laboratory test results will be evaluated:
  - Clinical chemistry: alanine aminotransferase, aspartate aminotransferase, creatinine, sodium, potassium, chloride, C-reactive protein, γ-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, eosinophils).

### *PK Outcome Measures*

- The systemic concentration of ALX-0171 will be evaluated in serum.

### *Antiviral Effect Outcome Measures*

- Quantification of viral titers (in mid-turbinate nasal swab samples) over time.

### *Clinical Activity Outcome Measures<sup>†</sup>*

<sup>†</sup> The evaluation of several of these parameters will also inform on safety outcome.

- Heart rate, respiratory rate (measured over a 1-minute interval) and SpO<sub>2</sub>.
- Feeding: type of feeding support, and (time and date of) sufficient feeding to allow for hospital discharge, in the opinion of the Investigator (with particular attention to hydration and breathing comfort during feeding)
- Wheezing as assessed during lung auscultation
- Cough during the night and during the day
- Respiratory muscle retractions (supraclavicular, intercostal, and subcostal)
- General appearance: activity, irritation, and responsiveness
- Body temperature and body weight
- Occurrence of apnea episodes

#### *Medical Interventions Outcome Measures<sup>†</sup>*

- Length of hospital stay for RSV infection
- Level, method, and duration of supplemental oxygen therapy
- Initiation of invasive or non-invasive ventilation (e.g., continuous positive airway pressure [cPAP] or HFOT)
- Level, method and duration of invasive or non-invasive ventilation
- Transfer to ICU and duration of stay in ICU

The clinical impact of treatment by ALX-0171 in infants and young children will be evaluated by changes in clinical symptoms (SpO<sub>2</sub>, feeding, respiratory rate, wheezing, cough, respiratory muscle retractions, and general appearance) and subsequent calculation of composite scores (Global Severity Score, Respiratory Distress Assessment Instrument [RDAI] score, and Respiratory Assessment Change Score [RACS]), the time needed to enable adequate feeding and oxygen saturation (clinical response) to allow for hospital discharge, need for medical interventions and length of hospital stay.

#### *Parent/Caregiver Outcome Measures*

Parent(s)/caregiver(s) assessment of the clinical condition of the child will be done by daily completion of a diary during the hospital stay and up to the EOS (Day 28) visit. This diary includes scoring of respiratory symptoms (cough, wheezing, trouble breathing) over the preceding 24 hours, evaluating the general health of the child by completing a Visual Analogue Scale (VAS), and answering a question as to whether the child has returned to his/her normal condition from before the onset the RSV infection. For the period after discharge from the hospital, this diary will also allow to capture data on health care utilization and use of medication for respiratory symptoms.

#### *Immunogenicity*

Systemic presence (serum) of anti-drug antibodies (ADA).

### *PD Outcome Measures*

Exploratory evaluation of the biomarker Krebs von den Lungen-6 (KL-6) in serum.

## **Statistics**

### *Sample size*

A total of 60 subjects will be randomized and treated in this study. The sample size was selected to provide sufficient safety and tolerability experience with ALX-0171 in this population, to confirm the safety profile reported in the studies conducted outside of Japan. The sample size provides sufficient precision on the PK parameters as described by Wang et al., 2012<sup>‡</sup>, and is expected to be informative on antiviral and clinical activity of ALX-0171 (descriptive analysis).

### *Statistical Analysis*

Data will be summarized by descriptive statistics as applicable (number of observations, mean, standard error, median, minimum and maximum for most continuous data; frequencies and percentages of categorical data, as appropriate). For time-to-event measures, the number and percentage of subjects achieving the event will be summarized by treatment. Kaplan-Meier estimates for the time-to-event will be presented for each treatment group.

Analysis of all parameters will be described in a Statistical Analysis Plan (SAP) and a Data Analysis Plan (DAP; for PK analysis), which will be finalized prior to database lock, and will comprise all methods applied for analysis of the corresponding data. There will be no interim analysis performed in this study.

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<sup>‡</sup> Wang, Y., et al., *Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies*. Journal of clinical pharmacology, 2012. **52**(10): p. 1601-6

## SCHEDULE OF ASSESSMENTS

Period  Visit	Screening <sup>a b</sup>	Study Drug Treatment Period <sup>c</sup>												In-hospital Post-Treatm. Period <sup>d</sup>	FU Visit (Day 14 ± 2) or Withdrawal Visit	EOS <sup>e</sup> (Day 28±2)	
		Hospitalized Dosing															
		Day 1				Day 2				Day 3				Morning and Evening			
Time window / Study procedure	-24h to randomization	-3h <sup>a</sup> to dose	Dose	2h (± 0.5h)	5h (±1h)	-2h to dose	Dose	2h (± 0.5h)	5h (±1h)	-2h to dose	Dose	2h (±0.5h)	5h (±1h)				
Informed consent	X																
Inclusion / exclusion criteria	X																
RSV diagnosis <sup>f</sup>	X																
12-lead ECG	X																
Demographics and medical history	X																
Previous medications	X																
Hospitalization info. <sup>g</sup>	→																
Study drug admin. <sup>i</sup>			X				X				X						
Nasal mid-turbinate swab <sup>j</sup>		X <sup>j</sup>			X	X			X	X			X	X <sup>k</sup>	X		
Physical examination <sup>l</sup>	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		
Lung auscultation <sup>o</sup>	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> <sup>m</sup>	X	X		X	X	X		X	X	X		X	X	X			
Feeding <sup>n</sup>	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		X <sup>b</sup>															
Clinical response information <sup>h</sup>		→															



<div>Period</div> <div>Visit</div>	Screening <sup>a b</sup>	Study Drug Treatment Period <sup>c</sup>												In-hospital Post-Treatm. Period <sup>d</sup>	FU Visit (Day 14 ± 2) or Withdrawal Visit	EOS <sup>e</sup> (Day 28±2)
		Hospitalized Dosing												Morning and Evening		
		Day 1				Day 2				Day 3						
Time window / Study procedure	-24h to randomization	-3h <sup>a</sup> to dose	Dose	2h (± 0.5h)	5h (±1h)	-2h to dose	Dose	2h (± 0.5h)	5h (±1h)	-2h to dose	Dose	2h (±0.5h)	5h (±1h)			
Daytime coughing	X	X		X	X	X		X	X	X		X	X	X <sup>p</sup>	X	X
Sleep disturbance from night-time coughing <sup>q</sup>	X	X				X				X				X	X	X
Parent/caregiver assessment <sup>r</sup>																
Pharmacokinetics						X <sup>s</sup>	<div>←<sup>s</sup>→</div>		<div>←<sup>s</sup>→</div>							
Clinical laboratory (hematology and clinical biochemistry)	X <sup>t</sup>														X <sup>u</sup>	
Immunogenicity <sup>v</sup>	X <sup>w</sup>														X <sup>u,x</sup>	
Concomitant medications																
Adverse events <sup>y</sup>																

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

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

- At the time of screening, all screening assessments are to be performed. If Day 1 pre-dose timing occurs within 3 hours after screening, the assessments already done at screening do not need to be repeated; only the remaining Day 1 (pre-dose assessments) will need to be performed.
- 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 and dosing, unless these assessments were already performed within the last 3 hours before randomization.
- Study drug administration should take place within 24 hour intervals (±4 hours) relative to the start of the first dose. For subjects requiring 2 serial nebulizations (subjects weighing ≥10 kg in the 9 mg/kg dose group), the timing of study drug administrations should be relative to the start of their first nebulization. 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 on Day 3 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.
- 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.
- For subjects who discontinue the study before Day 14, the Withdrawal visit will be conducted on the day of withdrawal as long as there has been no withdrawal of consent, subject is lost to follow-up or death. 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 (polymerase chain reaction [PCR], immunofluorescence 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.
- h. Assessment of Clinical Response will be done with collection of date and time of adequate oral feeding, as well as stable adequate oxygen saturation on room air of  $\geq 95\%$  over a period of at least 4 hours to allow for hospital discharge.
- i. Study drug will be administered via nebulization using the study-specific device.
- j. A mid-turbinate nasal swab should be taken using provided kits and following specific instructions. Collection of nasal swab samples from both nostrils is preferred. The nasal swab sample collected pre-dose on Day 1 will also be used to test for concurrent viruses and the presence of mycoplasma at baseline. Additionally, mid-turbinate nasal swab samples should be taken in case the subject is re-hospitalized or when the Investigator is consulted for a respiratory condition after hospital discharge.
- k. A mid-turbinate nasal swab should be collected during the in-hospital post-treatment period on the day of hospital discharge. A mid-turbinate nasal swab must also be taken in case the subject is re-hospitalized or when the Investigator is consulted for a respiratory condition after hospital discharge. Collection of nasal swab samples from both nostrils is preferred.
- l. Physical examination includes heart auscultation, examination of abdomen, skin and ears/nose/throat. Lung auscultation is listed separately as it is to be assessed more frequently.
- m. Continuous monitoring of  $\text{SpO}_2$  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.
- n. Type of feeding support, if any, and feasibility of oral feeding.
- o. To assess wheezing, crackles/crepitation and other abnormalities in lung auscultation.
- p. During the in-hospital post-treatment period, daytime coughing should only be recorded in the evening of the same day.
- q. 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, 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.
- r. The parent/caregiver assessment should be performed for the first time at screening and afterwards every evening until the EOS visit by completing a diary.
- s. All subjects will undergo PK analysis sampling (3 PK samples per subject), i.e., blood draws on Days 2-3: 1) pre-second dose, 2) between 0.5 hours and 3 hours post-second dose and at least 1 hour apart from the first sampling, and 3) 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.
- 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. No blood sample needs to be taken in case of premature withdrawal from the study for subjects who did not receive any study drug.
- v. For subjects with a body weight below 5 kg and in case the blood volume needed for local clinical laboratory exceeds 2.5 mL, the sample for analysis of immunogenicity should not be collected at screening and on Day 14, but on Day 1 pre-dose and on Day 28, if possible.
- w. 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 time point, if possible.
- x. 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 on Day 14, the sample should be collected at the EOS (Day 28) visit, if possible.
- y. An additional serum sample should be collected (if reasonably feasible) in case a serious and/or severe hypersensitivity reaction judged to be related to study drug occurs.

# 1. INTRODUCTION

Respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is a leading cause of bronchiolitis in infants and results in over 3 million hospitalizations worldwide per year. ALX-0171 is a therapeutic protein (Nanobody) that is currently being developed for the treatment of RSV LRTI.

The antiviral effect of ALX-0171 is expected to provide rapid control of the infection, thereby reducing the intensity and duration of severe disease. The favorable *in vitro* potency of ALX-0171 Nanobody and the *in vivo* results obtained in nonclinical studies indicate that ALX-0171 may provide an opportunity for therapeutic intervention in established RSV infection. This is also supported by an initial clinical study in children hospitalized for RSV LRTI, where treatment with inhaled ALX-0171 had an immediate impact on viral replication and reduced viral load compared to placebo.

## 1.1. TREATMENT OF RSV LRTI

Nearly all infants are infected with RSV over the first years of life. RSV LRTI is associated with significant morbidity and mortality [1, 2]. RSV infection imposes a significant burden on health care infrastructure and there is a high unmet medical need for treatment options. Evidence-based guidelines indicate that there are no treatments that shorten the course of bronchiolitis or hasten the resolution of symptoms; supportive care (hydration and oxygen saturation) remains the cornerstone of clinical management [1, 3, 4].

## 1.2. ALX-0171

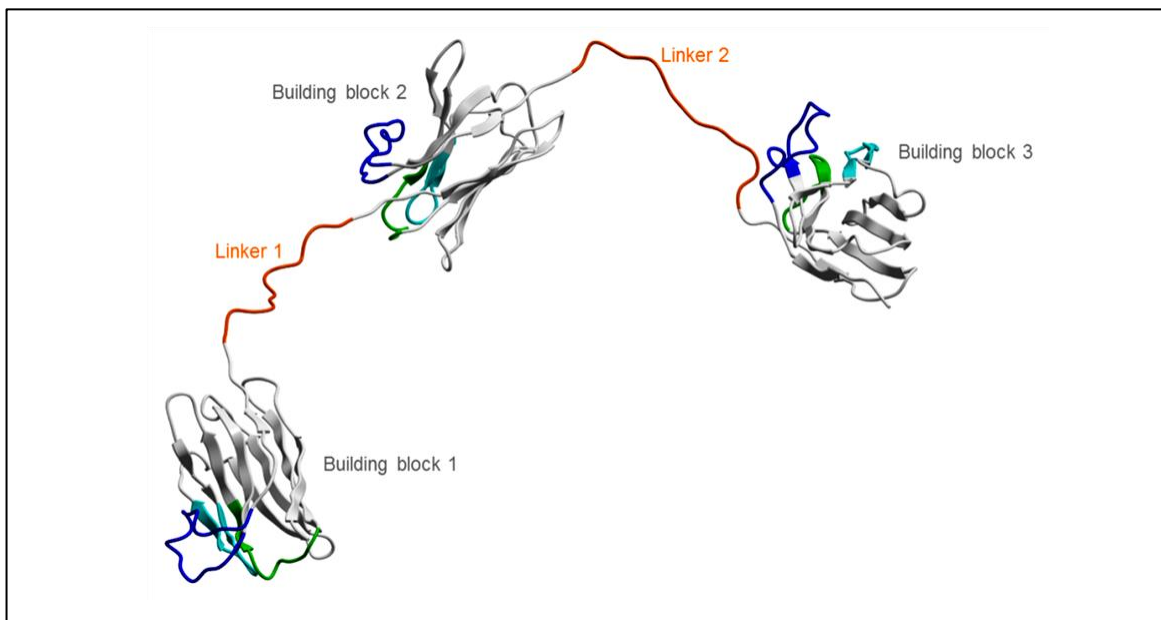
Nanobodies are a novel class of therapeutic proteins, and are based on the smallest functional fragments of single-chain antibodies that occur naturally in the *Camelidae* family. ALX-0171 Nanobody is directed towards the RSV fusion (F) protein, and is intended to interfere with viral entry into host cells. ALX-0171 is a trivalent Nanobody, formed by three identical building blocks connected via two linkers (Figure 1). All three moieties are capable of binding to the homotrimeric RSV F protein.

The F protein is highly conserved between RSV serotypes, and is therefore considered the main target for development of viral entry inhibitors. Following activation, the RSV F protein causes the membranes of the host cell and the virion to come into close vicinity and fuse together, allowing further infection and viral replication. Glycoprotein F also induces fusion of infected cells with adjacent, uninfected cells (epithelial cell syncytia), which allows for cell-to-cell transmission of the replicated viral RNA and confers additional protection against host immune responses [5].

ALX-0171 Nanobody binds to a well-conserved epitope in antigenic site II of the RSV F protein, close to or overlapping with the epitope of the clinical benchmark palivizumab

(trade name Synagis®, MedImmune/AstraZeneca). The latter is a humanized monoclonal antibody (mAb) indicated for the prevention of serious lower respiratory tract disease in high risk children, and is prophylactically administered by monthly intramuscular injections throughout the RSV season.

**Figure 1: Schematic representation of ALX-0171 Nanobody**



The amino acid (15-GS) linkers connect the C-terminus of the first building block with the N-terminus of the second one, and the C-terminus of the second building block with the N-terminus of the third one. The three building blocks (designated RSVNMP1A4) are identical, with the only exception of the E1D mutation in the first building block, which has been introduced to avoid pyroglutamate formation.

### 1.2.1. PHARMACEUTICAL PROPERTIES

Since direct delivery and deposition in the respiratory tract is desirable, inhalation was considered the preferred route of administration. ALX-0171 was therefore developed as a solution for nebulization, containing 50 mg/mL ALX-0171 Nanobody dissolved in a formulation buffer suitable for inhalation.

ALX-0171 solution for nebulization is administered using the handheld FOX-Flamingo inhalation system. The FOX-Flamingo is intended for professional use in a clinical environment, in spontaneously-breathing subjects from birth up to 3 years.

## 1.2.2. NONCLINICAL STUDIES

### Pharmacological properties

- ALX-0171 was characterized using *in vitro* systems, including assessment of affinity, biological activity and specificity. Different cellular systems of RSV replication were used, with cell-line adapted virus strains as well as viruses isolated from clinical cases.
- *In vivo* efficacy was demonstrated in the RSV infection cotton rat model, a standard model used in the field. Intranasal and intratracheal administration and nebulization were used to reflect the clinical route of administration.
- Efficacy and safety were further confirmed in the neonatal lamb model of RSV infection, a disease model that allows the assessment of clinical symptoms, histopathology and viral titers, and more closely mimics the clinical situation in infants.

### Safety pharmacology

Specific Good Laboratory Practice (GLP) -compliant *in vivo* studies were designed for the evaluation of ALX-0171 effects on respiratory and cardiovascular system, in rats and dogs respectively.

### Pharmacokinetics

The objective of the Pharmacokinetic (PK) program was the characterization of plasma and local (lung) kinetics of ALX-0171 in nonclinical toxicity studies. Additionally, the impact of anti-drug antibodies (ADA) on the PK of ALX-0171 was evaluated. PK parameters were also derived from a study in juvenile rats after single or repeated dose inhalation (starting from post-natal dose 4), as well as from an efficacy study in neonatal lambs. The latter includes information from infected animals.

### Toxicology

Two 14-day repeat-dose toxicity studies in rats, after once-daily administration via inhalation and via intravenous (i.v.) administration respectively, showed no treatment-related effects on local tolerance, clinical signs, body weight, food consumption, ophthalmic examination, hematology and coagulation, clinical chemistry, urine analysis, macropathology, histopathology, or organ weights.

Safety evaluations were included in the studies involving RSV-infected cotton rats and neonatal lambs.

The risk of accidental exposure of the face, and particularly of the eyes, during nebulization via a face mask, was assessed nonclinically. No local irritant effects of ALX-0171 on bovine cornea were observed. Likewise, in a repeated dose PK study in juvenile rats after inhalation, no clinical signs indicative of eye irritation or histopathology findings were reported.

## **1.2.3. EFFECTS IN HUMANS**

### **1.2.3.1. OVERVIEW**

At present, three Phase 1 clinical trials have been conducted in adults, to obtain initial safety and PK data. Following completion of the adult studies, a first-in-infant clinical study was recently completed. A Phase 2b pediatric trial is currently ongoing outside of Japan. Please refer to the Investigator's Brochure (IB) for a detailed overview of each of the individual studies:

- First-in-man Phase 1 study ALX-0171-1.1/11 (N=60) evaluated the safety, tolerability and PK of ALX-0171, administered by inhalation, in healthy male volunteers.
- Phase 1 study ALX-0171-1.3/13 (N=44) was performed to obtain additional information on local and systemic PK of ALX-0171 in healthy male volunteers.
- Phase 1 safety study ALX-0171-1.2/13 (N=24) evaluated the potential occurrence, reversibility and prevention of bronchoconstriction upon inhalation of ALX-0171 by adults with sensitive (hyperresponsive) airways.
- Study ALX0171-C104 (N=53) was a Phase 1/2a multicenter study in infants and young children hospitalized for RSV LRTI, to provide an initial evaluation of the safety, tolerability, antiviral and clinical activity of ALX-0171.
- Phase 2b dose-ranging study ALX0171-C201 (currently ongoing outside of Japan) aims primarily to evaluate the antiviral effect of three doses of inhaled ALX-0171, as well as to assess the safety and clinical activity, in RSV-infected infants and young children hospitalized for RSV LRTI.

### **1.2.3.2. CLINICAL SAFETY**

#### **1.2.3.2.1. ADULTS**

The completed clinical studies in adults showed that inhaled ALX-0171 was well-tolerated at all doses evaluated.

- Treatment-emergent adverse events (TEAEs) resolved quickly without further treatment, and were generally of mild to moderate intensity. The most common study drug-related TEAEs reported in the Phase 1 studies in adults included headache, rhinitis, oropharyngeal pain, cough, chest discomfort, throat irritation and wheezing (the latter in adults with hyperresponsive airways), generally of mild intensity.
- No study drug-related TEAEs leading to withdrawal were reported. Similarly, no study drug-related, clinically significant findings were observed with respect to clinical laboratory parameters, vital signs, electrocardiogram (ECG), physical examinations, or lung auscultations.
- In the studies in healthy volunteers, no meaningful trends in spirometry parameters were observed. The study in adults with hyperresponsive airways demonstrated the

reversibility of bronchoconstriction with bronchodilator treatment ( $\beta_2$ -agonist) and prevention with prophylactic use of bronchodilator.

#### **1.2.3.2.2. PEDIATRIC SUBJECTS**

In completed study ALX0171-C104, ALX-0171 was also found to be well-tolerated in infants and young children hospitalized for RSV LRTI.

- In line with the underlying disease, the most frequent TEAEs in study ALX0171-C104 were thoracic and mediastinal disorders, infections and infestations, and skin disorders. Possibly-related TEAEs occurred in 3 subjects (8.6%) in the ALX-0171 group. These were cough, rhinorrhea, and pyrexia. All were mild and resolved. None of the subjects in the placebo group showed possibly-related TEAEs.
- There were no treatment-related serious adverse events (SAEs) in this study. Five SAEs were reported in 4 subjects (11.4%) in the ALX-0171 group. These were hyporesponsiveness and hypotonia (both in 1 subject), pneumonia (2 subjects), and atelectasis. All resolved.
- Two subjects (5.7%) in the ALX-0171 group were prematurely discontinued from study drug (due to SAEs hypotonia and hyporesponsiveness and pneumonia). As noted above, all SAEs resolved. None of the subjects in the placebo group discontinued treatment.

#### **1.2.3.3. CLINICAL PHARMACOKINETICS**

In adults, the local (epithelial lining fluid) and systemic exposure levels were above the target for infants and young children, with good tolerability.

Consistent with lung exposure, inhaled ALX-0171 was quantifiable in the serum of most of the infants and young children in study ALX0171-C104.

#### **1.2.3.4. CLINICAL ACTIVITY AND PHARMACODYNAMICS**

Study ALX0171-C104 provided a first indication of antiviral and clinical activity in a relevant clinical setting, i.e., hospitalized infants with RSV LRTI.

- Data on nasal viral load indicates that ALX-0171 treatment rapidly and sustainably reduces cultivatable virus titers to below the quantification limit.
- Post-hoc 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.

### **1.2.3.5. IMMUNOGENICITY**

While immunogenicity has been reported in clinical studies with ALX-0171, no correlation with potential immune-related AEs has been established thus far, neither in adults nor in RSV-infected children.

- In adults, pre-existing antibodies (pre-Ab<sup>§</sup>) were found in 7% (ALX-0171-1.1/11) to 18% (ALX-0171-1.3/13) of the subjects.
- In the Phase 1 study ALX0171-1.1/11, no treatment-emergent ADA (TE ADA) responses were detected, whereas in the Phase 1 studies ALX-0171-1.3/13 and ALX-0171-1.2/13, TE ADA were observed in the serum of 13%-33% of the subjects, respectively.
- In Study ALX0171-C104, pre-Ab were found in 45% of the subjects, while TE ADA was detected in 23% of the infants. Pre-Ab detected in those children may reflect maternal antibodies transferred to the infant via the transplacental route during gestation or during breastfeeding. As the assay cannot discriminate pre-Ab from drug induced TE ADA, it is not clear to what extent the TE ADA detected may represent fluctuating levels of pre-Ab. Currently it is not known to what extent pre-Ab can fluctuate within the short study period (14 days). No effect of ADA on PK was observed.

TE ADA is not expected to have an impact on PK or efficacy given the short treatment duration, as TE ADA do not emerge in considerable amounts within the first 7 days after initial drug administration. It is also unlikely that the pre-existing or TE ADA against ALX-0171 would result in a clinically meaningful safety risk (see section 1.3.2 below).

## **1.3. SAFETY PROFILE AND BENEFIT-RISK ASSESSMENT**

The potential benefits and risks for administration of ALX-0171 are assessed from the available nonclinical data and the results of the completed Phase 1 clinical studies in adults and a Phase 1/2a trial in children hospitalized for RSV LRTI.

### **1.3.1. NONCLINICAL RESULTS**

Detailed nonclinical assessment of systemic toxicity as well as local tolerability and respiratory safety revealed no clinically meaningful risks for administration of ALX-0171 to pediatric subjects. The results were consistent across the different nonclinical safety and toxicology studies.

<sup>§</sup> Pre-existing antibodies, i.e., ADA present in samples from treatment-naïve subjects, have been commonly observed during immunogenicity assessments.



## 1.3.2. CLINICAL SAFETY RESULTS

At present, three Phase 1 clinical studies have been completed in adults. In addition, a Phase 1/2a study in children aged 28 days to <2 years hospitalized for RSV LRTI was recently completed. ALX-0171 was generally well tolerated in all clinical studies.

## 1.3.3. POTENTIAL RISKS

ALX-0171 has no endogenous target and no secondary pharmacology was noted throughout the pre-clinical development program; potential risks related to the pharmacology or to the mechanism of action of the compound are therefore considered unlikely.

More general risks, inherent to administration of inhalation products or therapeutic proteins, cannot be excluded. A continuous further evaluation is included during clinical development to assess if these potential effects would constitute clinically meaningful risks for administration of ALX-0171.

### Airway Hyperresponsiveness

Viral respiratory infections are known to transiently increase bronchial reactivity, potentially leading to airway hyperresponsiveness (i.e., an abnormal airway narrowing of the bronchi, triggered by various chemical or physical stimuli).

The occurrence, treatment and prevention of potential bronchoconstriction subsequent to ALX-0171 inhalation was evaluated in a dedicated Phase 1 study in adults with hyper responsive airways (Study ALX-0171-1.2/13). In total, 24 subjects participated in the study. In this population, 10 subjects (42%) experienced a mild to moderate bronchoconstriction either during the escalating dose or repeated dose part of the study. All events were treated successfully with  $\beta_2$ -agonist (salbutamol). The results of this study demonstrated the immediate reversibility of bronchoconstriction with bronchodilator treatment ( $\beta_2$ -agonist) and prevention with prophylactic use of bronchodilator.

In the first-in-infant Study ALX0171-C104, as a precaution and in order to standardize treatment across the sites, an inhaled dose of the short-acting  $\beta_2$ -agonist salbutamol was administered before each administration of study drug. A review of the safety data and respiratory parameters collected in the first-in-infant study did not reveal a bronchoconstrictive risk after study drug inhalation. Therefore, the requirement for prophylactic administration of a  $\beta_2$ -agonist is not implemented in the current protocol, but the use of bronchodilator treatment is permitted at the Investigator's discretion. The same approach is used in ongoing Phase 2b study ALX0171-C201.

The potential risks of airway hyperresponsiveness and bronchoconstriction will be closely monitored in each of the cohorts, including via regular Independent Data Monitoring Committee (IDMC) review.

### Immediate or Delayed Adverse Drug Reactions

All therapeutic proteins have the potential to elicit antibody or other immune- or non-immune-mediated responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness and anaphylactoid or anaphylactic reactions. These responses are complex and could occur following initial or only after repeated exposure, and are very difficult to predict.

Within the context of the planned clinical study, immunogenicity-related AEs as a consequence of TE ADA are not expected, as TE ADA typically do not emerge in considerable amounts earlier than 7 days after first administration of study drug, at times where study drug is expected to be cleared, given the short treatment period of 3 days.

While pre-Ab and TE ADA have been reported in clinical studies with ALX-0171, no correlation with potential immune-related AEs has been established thus far in adults or in RSV-infected children. No immune response-related toxicological findings were reported during the nonclinical studies.

- During Study ALX-0171-1.3/13, a possible mild hypersensitivity reaction (unilateral eyelid oedema) was noticed in one subject approximately 1 hour after 1 single i.v. dose. No pre-Ab or TE ADA were detected in this subject.
- During Study ALX0171-C104, no correlation between immunogenicity (either pre-Ab or TE ADA) and safety was seen. One subject with a history of acute urticaria presented with a mild exanthema of abdomen, trunk, back and retroauricular area, about 5 hours after the second drug administration. The event resolved without medication and was considered unlikely/not related to the study drug by the Investigator. This subject was pre-Ab positive and TE ADA positive. A possible correlation with immunogenicity (pre-Ab and/or TE ADA) cannot be excluded for this subject.

The potential immunogenicity of ALX-0171 has not yet been evaluated in Japanese subjects. In line with regulatory and scientific guidance, an immunogenicity risk assessment [6] was prepared for administration of ALX-0171, in support of the currently proposed study [7-9]. This assessment comprised evaluation of the immunogenic potential of ALX-0171 through determination of product-specific, patient- and/or disease-related factors affecting immunogenicity. In addition, the available nonclinical and clinical immunogenicity results were evaluated to come to an appraisal on the potential consequences on safety, PK and efficacy in case immunogenicity would occur in the current pediatric study. The overall risk assessment led to a "lower risk class" designation (the lowest category for a therapeutic protein) [8], with favorable risk/benefit balance for the current pediatric study. Of note, the immunogenicity risk assessment is a dynamic process, with further evaluations and updates scheduled as data become available [10].

### Unintentional Contact/Exposure

To ensure correct administration of ALX-0171 and handling of the device, detailed instructions for use will be provided. During administration by nebulization, caregivers or other persons close to the nebulizer may nevertheless come into contact with ALX-0171. This may for instance occur due to aerosol escaping through the outlet valves of the facemask, or via particles exhaled by the subject. This is not considered to pose a safety risk. ALX-0171 is highly specific towards the RSV F protein, and lacks an endogenous human target. The *in vivo* safety pharmacology and toxicology studies revealed no meaningful safety risks. As described above, the clinical studies conducted so far showed that ALX-0171 was well tolerated at all dose levels and dosing regimens evaluated. In addition, no teratogenic or oncogenic properties are expected. As ALX-0171 is a protein drug, it is not expected to enter cells and interfere directly with DNA or nuclear proteins.

Furthermore, Investigators, clinical staff, parents, family members or other children in the vicinity would only come in contact with ALX-0171 at a negligible dose<sup>\*\*</sup>. Potential deposition of aerosol particles onto surfaces, or unintentional contact by means other than inhalation, is not of concern. Similar to other proteins or macromolecules, standard hospital or household hygiene procedures are considered sufficient for cleaning of surfaces. There is no added risk for contact with skin, since ALX-0171 does not cause irritation, and is not prone to transdermal delivery (similar to other macromolecules). Exposure to mucosal tissues may be more relevant, but there are no indications that this would be associated with additional safety concerns, systemic uptake, or irritative effects. Finally, in case of accidental oral intake, ALX-0171 would be rapidly degraded in the digestive tract, similar to other proteins.

Routine hygiene conditions and cleaning procedures in the hospital are therefore sufficient for administration of ALX-0171. In view of the above, potential risks associated with unintentional contact are considered negligible. It should also be noted that, while not considered necessary, a standard facemask would be sufficient to further limit unintentional contact with ALX-0171 for the person administering study drug.

## 1.3.4. POTENTIAL BENEFITS

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 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].

<sup>\*\*</sup>Calculated "worst case" scenarios (e.g., 1-hour stay after administration of ALX-0171 in an examination room of 5 m<sup>2</sup> with poor ventilation, and assuming that the entire dose filled into the nebulizer is dissipated into the room) indicate that inhalation of dissipating aerosol by any person (adult or infant) other than the intended subject would result in an ALX-0171 dose at least 100-fold below the nebulized dose. Of note, in case only incomplete or inefficient administration is achieved (e.g., because of poor fitting of the face mask, or because of intense crying of the subject), nebulization is to be stopped, thereby avoiding unwanted loss of study drug into the room.

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). 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.

Analysis of a composite of clinical parameters from the first-in-infant study, the Global Severity Score, led to an encouraging initial indication of a therapeutic effect for infants treated with ALX-0171 and given its favorable safety profile from clinical studies to date, further evaluation of the agent is being pursued.

### 1.3.5. CONCLUSION

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 current Phase 2 study in Japanese infants and young children, study ALX0171-C203, will evaluate dose levels investigated in the completed first-in-infant study ALX0171-C104 and the ongoing Phase 2b, dose-ranging study ALX0171-C201. The doses are estimated to achieve concentrations at which antiviral and clinical activity can be expected while appropriate safety margins are respected. The dose range is therefore expected to provide a potential benefit to the subjects, and is intended to support selection of an optimal dose of ALX-0171 for further clinical development, taking ethnicity into consideration.

Regular review of clinical data by the IDMC before initiation of a higher dose, including pauses in recruitment, will enable adequate safety follow-up throughout the study. The clinical study protocol foresees close monitoring of all subjects, and is considered to provide a suitable setting for evaluation of ALX-0171 in infants and young children.

In view of the above, the current benefit/risk assessment is therefore considered favorable and supportive of further clinical development.

## 2. OBJECTIVES

The objectives of this study are:

- to evaluate the safety, tolerability, and systemic PK of different doses of inhaled ALX-0171 in Japanese infants and young children hospitalized for RSV LRTI.
- to evaluate the antiviral effect, clinical activity, immunogenicity, and PD of different doses of inhaled ALX-0171 in Japanese infants and young children hospitalized for RSV LRTI.

## 3. STUDY DESIGN

### 3.1. OVERALL STUDY DESIGN

#### 3.1.1. STUDY OVERVIEW

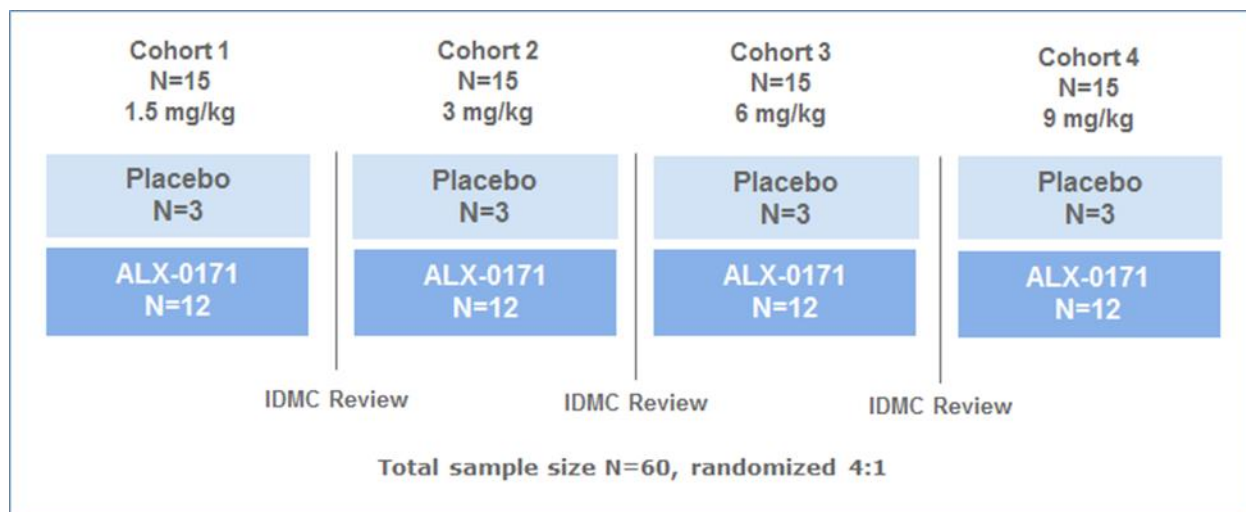
Study ALX0171-C203 is a randomized, double-blind, multicenter, multiple-dose study of ALX-0171 versus placebo along with standard of care in Japanese infants and young children aged 28 days to <2 years hospitalized for RSV LRTI. A schematic of the study design presented in [Figure 2](#).

The overall study duration is expected to be approximately 12 months, with the planned study duration for each subject approximately 28 days.

The following dose levels are planned to be evaluated in four consecutive cohorts:

- Dose 1: target dose of 1.5 mg/kg
- Dose 2: target dose of 3.0 mg/kg
- Dose 3: target dose of 6.0 mg/kg
- Dose 4: target dose of 9.0 mg/kg

Each cohort will consist of 15 subjects enrolled, randomly assigned to and received ALX-0171 or placebo, in an allocation ratio of 4:1 (N=12 active versus N=3 placebo per cohort). Study drug will be administered once daily for 3 consecutive days and will be given along with standard of care treatment, which will be determined by the Investigator according to institutional practice (taking into account the prohibited medications listed in [section 3.3.7](#)). The 3-day treatment period is expected to bridge the time needed for the body to mount an effective immune response.

**Figure 2: ALX0171-C203 – Study Design**

IDMC=Independent Data Monitoring Committee

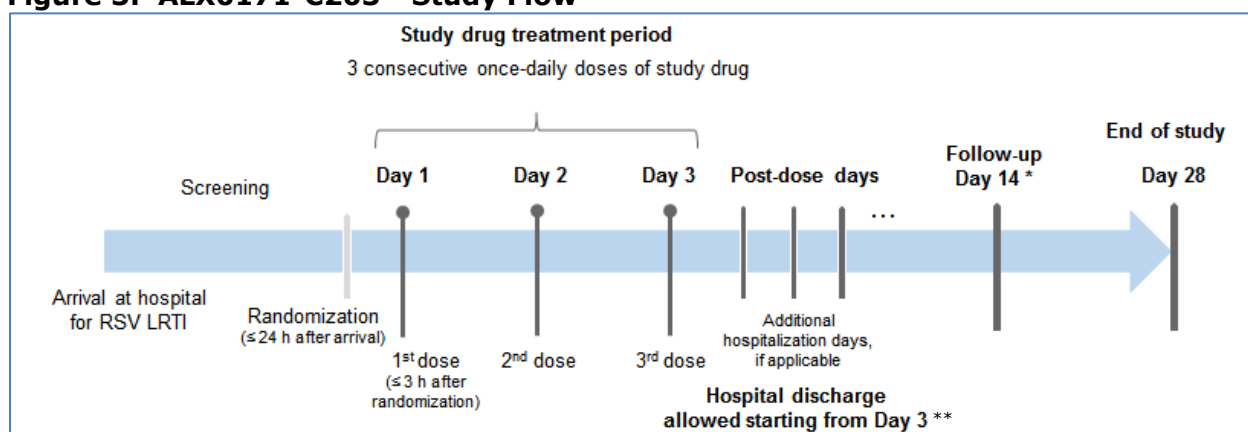
An overview of the study flow is shown in [Figure 3](#).

- Upon signing of the Informed Consent Form (ICF), subjects will be screened as soon as possible after arrival at the hospital/emergency unit. After completion of the screening assessments and confirmation of subject's eligibility, randomization should follow as soon as possible but not longer than 24 hours after arrival at the hospital/emergency unit.
- Study drug administration should start as soon as possible after randomization with a maximum time interval of 3 hours following randomization. Subsequent doses of study drug will be administered at 24-hour intervals ( $\pm 4$  hours) relative to the first dose. No pre-medication is required per protocol, but an inhaled  $\beta_2$ -agonist may be administered at the discretion of the treating Investigator.
- During the 3 treatment days, inpatient hospital stay is required.
- Discharge from the hospital can take place per protocol at the Investigator's discretion from dosing on Day 3 onwards, after all required assessments of the 5 hours ( $\pm 1$  hour) post-dose time point have been completed and provided that the clinical response criteria have been met. Subjects who are not discharged from the hospital after completion of the treatment period will enter an in-hospital post-treatment period with assessments in the morning and evening until discharged.
- 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).
- Unscheduled visits may be conducted to assess or follow-up on AEs or laboratory abnormalities. In such cases, the evaluations performed are at the discretion of the Investigator.
- An Unscheduled Visit is also to be performed in case a subject is re-hospitalized, or when the Investigator is consulted for a respiratory condition occurring after discharge from the hospital. In such cases, a mid-turbinate nasal swab is to be collected and a physical examination, including lung auscultation, must be performed.

- For subjects prematurely withdrawn from the study, a Withdrawal visit is to be performed on the day of withdrawal (unless the consent was withdrawn, subject is lost to follow up, or died) (see section 3.4).
- Subjects who discontinue study drug (for any reason) but remain hospitalized will enter the in-hospital post-treatment period and will be followed up twice daily (in the morning and the evening) until they are discharged from the hospital. They should also attend the FU and EOS visit.

After the end of the subject's participation in the study, each subject is to be treated according to standard clinical practice.

**Figure 3: ALX0171-C203 - Study Flow**



\*Or withdrawal visit at earlier time point in case of withdrawal

\*\*Hospital discharge is allowed from Day 3 once all post-dose assessments have been completed and clinical response criteria have been met.

### *Independent Data Monitoring Committee*

In line with applicable guidelines, an IDMC is assigned to monitor the study. The IDMC consists of an independent group of clinical experts. The participants, objectives, and roles and responsibilities of the IDMC will be described in an IDMC Charter. The IDMC Charter will also define and document the content of the safety summaries, and general procedures (including communications). The first version of the charter will be finalized prior to the initiation of the study.

After the last subject in a cohort has completed his/her treatment period or has discontinued study drug, the IDMC will review the available cumulative unblinded safety data (i.e., all available data for all included subjects, including preceding cohorts) and advise the Sponsor on proceeding to the subsequent cohort (i.e., the next higher dose). Recruitment will be paused during IDMC reviews.

SAE information will be communicated to the IDMC in real time throughout the study, as per the IDMC Charter. An ad-hoc meeting can be requested by the IDMC members at any time.



### *Dose Escalation Stopping Criteria*

In addition to the individual discontinuation criteria (see section 3.4), the following criteria apply to stopping or pausing recruitment:

1. Should an SAE indicative of acute respiratory distress or an acute systemic hypersensitivity reaction be considered by the Investigator to be related to administration of ALX-0171, recruitment in that cohort will be stopped and no further dose escalation will be done.
2. The reporting of any other SAE considered by the Investigator to be related to administration of ALX-0171 will trigger a pause in recruitment and an immediate review by the IDMC. Confirmation of the causality between the administration of ALX-0171 and the serious adverse reaction by the IDMC will result in the stopping of recruitment in that cohort and no further dose escalation will be done.
3. In case 2 SAEs considered by the Investigator to be possibly related to administration of ALX-0171 occur in the same cohort, recruitment in that cohort will be paused to allow further investigation by the IDMC. This includes assessment of the index events as well as review of any prior similar events, after which the IDMC will issue a recommendation regarding continuation or stopping of the paused cohort. In case recruitment is reinitiated based on the IDMC recommendation, the assessment for further dose escalation will be performed by the IDMC during the planned pause after completing the cohort, when the cumulative dataset is available.
4. If 2 severe adverse events (AEs) indicative of acute respiratory distress or an acute systemic hypersensitivity reaction would occur in a particular cohort and are considered by the Investigator to be related to administration of ALX-0171, no further dose escalation will be done.

## **3.1.2. STUDY RATIONALE AND DISCUSSION OF STUDY DESIGN**

Throughout the clinical program, inhalation of ALX-0171 was shown to be generally well tolerated. The encouraging results obtained in Study ALX0171-C104 (first-infant study) supported the initiation of a global Phase 2b dose-ranging study in non-Japanese infants and young children (aged 28 days to <2 years) hospitalized for RSV LRTI (N=180, study ALX0171-C201).

The present study, ALX0171-C203, is a double-blind, multiple-dose study of ALX-0171 versus placebo along with standard of care in Japanese infants and young children hospitalized for RSV LRTI. The RSV infection is confirmed by the Investigator's assessment of clinical criteria, and by virological confirmation (RSV diagnostic test).

The main objective of the study is evaluation of the safety, tolerability and PK of ALX-0171 compared to placebo. As pharmacologically active doses will be used, the antiviral effect,



clinical activity, and PD characteristics of ALX-0171 will also be evaluated, in addition to potential immunogenicity.

### *Study Population*

The first-in-infant study ALX0171-C104 provided a first confirmation of safety and tolerability of inhaled administration of ALX-0171 in infants and young children hospitalized for RSV infection. The children enrolled in this study were, besides their RSV infection, otherwise healthy, without significant co-morbidities and with a normal gestational age. Based on the reassuring safety profile observed in study ALX0171-C104, the Phase 2 studies performed with ALX-0171 include the age range from 28 days up to <2 years, which is a highly relevant age window for this indication [11].

Considering that the Phase 2 studies are also aimed at defining appropriate dose levels for further development, co-morbidities that would confound this assessment (e.g., clinically significant heart or pulmonary diseases) are still excluded. The eligible gestational age ( $\geq 33$  weeks) allows moderate to late ex-preterm infants to enter the study, which is an important subgroup for RSV infection [11]. Based on discussions with clinical experts, these infants are expected to behave similarly to the term infants when they have reached 28 days of age, and no other co-morbidities (which are exclusionary) are present.

The eligibility criteria in the protocol include restrictions on the type and intensity of ventilation. Only conventional oxygen supplementation through nasal cannula, head box, or face mask is allowed, since these can be continued during study drug administration (the FOX-Flamingo provides a 2 L/minute oxygen or air flow). More intense ventilation, typically used for more severely distressed infants, is part of the exclusion criteria. Critically ill infants in need of invasive ventilation or respiratory support with positive airway pressure cannot be enrolled in the study, because a different outcome and safety profile can be expected in this more severe subpopulation.

In order to enable the antiviral treatment to provide clinical benefit to the infants, the time between the start of the infection and initiation of treatment is kept as short as possible in study ALX0171-C203. The inclusion criteria therefore mandate a maximum of 4 days between the onset of symptoms of the RSV infection and screening at the hospital.

### *Ethnic Sensitivity*

To ensure that subjects in study ALX0171-C203 are representative of the Japanese population, they are required to be born in Japan, to Japanese parents, and to have Japanese maternal and paternal grandparents.

Safety, PK/ PD characteristics, or antiviral activity have so far been evaluated in non-Japanese pediatric patients. The Sponsor expects that the combined dataset of studies ALX0171-C104 and ALX0171-C201, together with the results from Japanese study

ALX0171-C203, will enable selection of an optimal dose for future development, including in Japanese children.

#### *Determination of Sample Size*

The planned sample size of 60 randomized and treated subjects was selected to provide sufficient safety and tolerability experience with ALX-0171 in this population, to confirm the safety profile reported in studies conducted outside of Japan. The sample size also provides sufficient precision on the model estimated PK parameters, as described by Wang et al. [12], and it is expected to be informative on antiviral and clinical activity of ALX-0171.

The purpose of including placebo (in addition to standard of care) is to assist in the interpretation of results, and not for a formal statistical comparison between active and control subjects.

#### *Dose Selection Rationale*

The study drug will be administered via nebulization once daily for 3 consecutive days, in the hospital setting. The 3-day dosing regimen for ALX-0171 was based on the PD and PK properties of ALX-0171 and the current knowledge on viral kinetics and clinical management of RSV infection. The treatment period is expected to bridge the time needed for the body to mount an effective immune response that will clear the virus, and to provide the optimal individual benefit/risk balance for the subjects.

The dose range proposed to be studied in ALX0171-C203 was selected based on the results of study ALX0171-C104 (Phase 1/2a first-in-infant study), and includes the doses currently being evaluated in ongoing study ALX0171-C201 (Phase 2b dose-range finding study conducted outside of Japan). Additional details on the dose selection rationale are available in section 3.3.2.

#### *Background Therapy*

Standard-of-care therapy will be given as background therapy to all subjects in study ALX0171-C203, in addition to ALX-0171 or placebo. This is because the management of RSV in nearly all settings is supportive, and the approach is consistent with all major pediatric societies' guidelines [1, 13].

Prior or concomitant administration of palivizumab, other investigational compounds for RSV infection, or systemic corticosteroids or the initiation of inhaled corticosteroids will not be allowed; these treatments could interfere with the evaluation of ALX-0171 and are not in line with the endorsed treatments of RSV infection in the target population.

### *Study Assessments*

The assessments which will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

Safety and tolerability will be assessed through AE collection, measurements of vital signs, peripheral capillary oxygen saturation (SpO<sub>2</sub>), physical examination, and laboratory parameters. Safety lab assessments are planned two times during the study (at screening and at the FU visit) and will be performed by the local laboratory in order to allow timely availability of the results. Furthermore, an IDMC will be involved in the regular review of the available safety data.

The systemic concentration of ALX-0171 in serum will be evaluated over time, as a surrogate for local (lung) concentrations.

Potential immunogenicity will also be assessed systemically (serum), both pre-dose and post-dose (14 days post-initial drug administration) and results will be correlated with PK, PD and safety findings.

Systemic levels of the serum biomarker Krebs von den Lungen-6 (KL-6) will be determined in left-over serum samples. Serum KL-6 was shown to indicate disease activity in various interstitial lung diseases and is believed to reflect the presence of alveolar damage [14, 15]. High serum KL-6 levels in RSV-infected infants correlate with low SpO<sub>2</sub> and need for oxygen administration [16]. These findings suggest that serum KL-6 is associated with the severity of RSV bronchiolitis, and that it may provide additional insight on potential treatment benefits.

The intended volume of blood to be withdrawn for each of the assessments is based on the minimum required volume for each of the respective analyses, and is in line with the volumes allowed per applicable guidelines [17-21].

Viral load will be assessed in samples obtained via nasal swabs collecting a mid-turbinate specimen, and will be quantified using plaque cultures (to evaluate replication-competent virus) and by RT-qPCR (to evaluate viral mRNA). Based on ALX-0171 mechanism of action, plaque cultures best reflects viral neutralization, whereas RT-qPCR is more sensitive, but also quantifies ALX-0171 neutralized viral particles that are unable to infect other cells, partially assembled virions, and whole and fragmented viral genome.

The clinical impact of treatment by ALX-0171 in infants and young children will be evaluated by changes in clinical symptoms (SpO<sub>2</sub>, feeding, respiratory rate, wheezing, cough, respiratory muscle retractions, and general appearance) and subsequent calculation of composite scores, the time needed to achieve adequate feeding and oxygen saturation (clinical response) allowing for hospital discharge, the need for medical interventions, and length of hospital stay.

Based on the clinical activity parameters measured during the study, composite scores that reflect the clinical status of the subject suffering from RSV will be calculated, including the Global Severity Score, Respiratory Distress Assessment Instrument (RDAI) score, and Respiratory Assessment Change Score (RACS).

- The Global Severity Score is based on a recent clinical score that allows categorization of infants with respiratory infections on 7 different parameters: feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnea, general condition and fever [22, 23]. It takes into account all clinically relevant aspects of an RSV infected subject.
- The RDAI is a scoring system based on the presence and severity of wheezing and respiratory muscle retractions.
- The RACS is based on the RDAI and adds a standardized score for the change in respiratory rate.

Given the importance of timing of the administration of this antiviral compound in the time course of the RSV infection, details on the time elapsed between onset of first clinical symptoms and start of treatment with study drug will be collected and analyzed. The need for medical interventions will be documented through collection of data on the need for and level of oxygen supplementation or respiratory support, need for transfer to intensive care unit (ICU), duration of stay in ICU and overall hospital stay.

In addition to the assessments performed by healthcare professionals, the study will also collect information on how parents or caregivers perceive the clinical condition of the child through daily completion of a diary. This diary includes scoring of respiratory symptoms (cough, wheezing, trouble breathing) over the preceding 24 hours, evaluating the general health of the child by completing a Visual Analogue Scale (VAS), and answering a question as to whether the child has returned to his/her normal condition from before the onset the RSV infection. For the period after discharge from the hospital, this diary will also capture data on health care utilization and use of medication for respiratory symptoms. The diary will be completed during hospital stay and daily thereafter up to the EOS (Day 28) visit as RSV induced bronchiolitis is often associated with continuing respiratory symptoms following hospitalization.

### **3.1.3. BLINDING**

In order to protect the integrity of the data, treatment assignment will be kept blinded for investigative sites, subjects, subject's parent(s)/legal guardian(s) and caregiver(s), site monitors, and other members of the study team, until after the final database lock (i.e., after the last subject has completed the final [EOS] visit and all data is considered clean). Identification of Sponsor and contract research organization (CRO) personnel who will have access to unblinded data (e.g., PK sample analysis team) during the course of the study will be documented prior to unblinding. The number of Sponsor personnel having access to the data will be limited.

### *Emergency unblinding procedure*

Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via the Interactive web/voice response system (IWRS/IVRS), which will be accessible 24 hours per day/7 days per week.

Unblinding by the Investigator should occur only in the event of an AE for which it is necessary to know the study drug allocated to determine an appropriate course of therapy for the subject. The Investigator should first discuss options with the Medical Monitor if possible with due consideration of the safety of the subject. If the Investigator must identify the treatment assignment of an individual subject, the Principal Investigator/sub-Investigator is to contact the IWRS/IVRS.

Subjects for whom the code has been broken by the Investigator will have to discontinue study drug treatment and subjects will be followed up according to the in-hospital post-treatment period (if applicable), FU visit and EOS visit.

## **3.2. SELECTION OF STUDY POPULATION**

Japanese infants and young children of both genders diagnosed with and hospitalized for RSV LRTI but otherwise healthy, are eligible for this study. A total of 60 subjects are planned to be randomized and treated in the study.

### **3.2.1. INCLUSION CRITERIA**

A subject will be eligible for study participation if he/she meets all of the following criteria at screening and randomization, unless specified otherwise.

1. Subject is a Japanese male or female infant or young child aged 28 days to <2 years with gestational age  $\geq$  33 weeks at screening.
2. Subject is of Japanese descent, i.e., born in Japan to Japanese parents and has Japanese maternal and paternal grandparents.
3. Subject weighs between  $\geq$  3.0 kg and <15.0 kg at screening.
4. Subject is otherwise healthy, but is hospitalized for and clinically diagnosed with RSV LRTI (bronchiolitis or broncho-pneumonia), i.e., showing typical clinical signs and symptoms such as tachypnea, wheezing, cough, crackles, use of accessory muscles and/or nasal flaring.
5. Subject has a positive RSV diagnostic test within 4 days of screening.<sup>††</sup>
6. Subject is expected to have to stay in the hospital for at least 24 hours (according to the Investigator's judgment at screening).
7. Symptoms likely related to RSV infection (i.e., the symptoms present need to be probably linked to the current RSV infection according to Investigator's judgment) have

<sup>††</sup> RSV infection will be confirmed either according to routine site practice (PCR, immunofluorescence or diagnostic quick test), or using a Sponsor-provided commercial kit.

appeared within 4 days of screening and are not yet improving at screening and randomization.

8. Subject fulfils at least two of the following RSV disease severity criteria at screening and randomization:
  - Inadequate oral feeding that requires feeding support (i.e., nasogastric tube or i.v. line),
  - Inadequate oxygen saturation defined as:
    - Oxygen saturation (SpO<sub>2</sub>) < 95% on room air or
    - Requiring oxygen supplementation to maintain adequate oxygen saturation with documented pre-supplementation value < 95%
  - Signs of respiratory distress defined as:
    - Respiratory rate ≥ 50 breaths per minute in infants up to 12 months of age, and ≥ 40 breaths per minute in children above 12 months and/ or
    - Moderate or marked respiratory muscle retractions
9. Subject has normal psychomotor development.
10. Parent(s)/legal guardian(s) provide written informed consent in accordance with locally approved consent process at screening.
11. The parent(s)/legal guardian(s) are able and willing to comply with the study protocol procedures.

### **3.2.2. EXCLUSION CRITERIA**

Subjects meeting any of the following criteria at screening or randomization will not be eligible for study participation.

1. Subject is known to have significant comorbidities including:
  - Genetic disorders (e.g., trisomy 21, cystic fibrosis),
  - Hemodynamically significant congenital heart disease (e.g., needing corrective therapy or inotropic support),
  - Bronchopulmonary dysplasia,
  - Any hereditary or acquired metabolic (bone) diseases,
  - Hematologic or other malignancy.
2. Subject is known to be human immunodeficiency virus (HIV)-positive. If the subject is < 6 months of age, known HIV-positivity of the mother is also exclusionary.
3. Subject is known to be immunocompromised.
4. Subject has or is suspected to have an active, clinically relevant concurrent infection (e.g., bacterial pneumonia, urinary tract infection). Concurrent acute otitis media is not exclusionary.
5. Subject has significant oral and/or maxillofacial malformations which would prevent proper positioning of the face mask.
6. Subject received invasive mechanical ventilation or non-invasive respiratory support (i.e., continuous or bilevel positive airway pressure) in the 4 weeks prior to screening.

7. During the current admission, subject is initially hospitalized in an ICU setting and/or received invasive mechanical ventilation or non-invasive respiratory support (i.e., continuous or bilevel positive airway pressure).
8. Subject is critically ill and/or is expected to require invasive mechanical ventilation, non-invasive respiratory support (i.e., continuous or bilevel positive airway pressure), or high-flow oxygen therapy (HFOT) at levels not enabling nebulization therapy according to the Investigator's judgment. High Flow oxygen, with a maximum flow of 2 L/kg/min, is permitted under the following conditions:
  - used as Standard of Care outside ICU setting
  - can be removed for study drug administration (Note: oxygen flow at 2 L/minute can be provided through the nebulizer)
9. Subject has received 1 or more doses of palivizumab or treatment or prophylaxis with any RSV antiviral compound (e.g., ribavirin, i.v. immunoglobulin, or any investigational drug or vaccine for RSV [including subject's mother who has been vaccinated against RSV]) at any time prior to screening.
10. Subject is required to continue or start systemic corticosteroid therapy. Subject on a maintenance therapy of inhaled corticosteroids will continue this treatment at the usual dose. Topical corticosteroids for skin disorders are permitted.
11. Subject has clinically meaningful abnormalities on a 12-lead ECG, which according to the Investigator's judgement does not allow participation of the subject in the study. A 12-lead ECG performed within 4 days of screening will be acceptable. If not yet available, the 12-lead ECG should be performed at the time of screening.
12. Subject is a child in care (i.e., a child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation). A child in care can thus include a child cared for by foster parents or living in a care home institution, provided that the arrangement falls within the definition above, but does not include a child who is adopted or has appointed legal representative(s).
13. Subject is currently participating in any other study with investigational drug or has received an investigational drug within 4 weeks or 5 half-lives of the concerned drug (whichever is longer) prior to screening.
14. Subject was previously enrolled in a clinical study of ALX-0171 (including the current Study ALX0171-C203).
15. Subject has a known hypersensitivity to the study drug or any excipient of the study drug.
16. Subject is considered by the Investigator to be ineligible to participate in the trial for safety reasons or any other concern.

## **3.3. TREATMENT OF SUBJECTS**

### **3.3.1. OVERVIEW OF TREATMENTS ADMINISTERED**

Eligible subjects will be randomly assigned to one of the following treatment groups:

- ALX-0171 dose level 1: target dose of 1.5 mg/kg
- ALX-0171 dose level 2: target dose of 3.0 mg/kg
- ALX-0171 dose level 3: target dose of 6.0 mg/kg
- ALX-0171 dose level 4: target dose of 9.0 mg/kg
- Matching Placebo

Study drug will be administered via inhalation, using a dedicated vibrating mesh nebulizer.

- Vibrating mesh type nebulizers are considered the most appropriate technology for nebulization of a therapeutic protein such as ALX-0171 Nanobody.
- The FOX-Flamingo nebulizer (Vectura GmbH, Germany) was developed concurrently with the study drug. The nebulizer is a battery-operated, hand-held device, intended for single-patient use. The device provides an aerosol with particle size suitable for the intended study population ( $\sim 3 \mu\text{m}$ ).
- The nebulizer is always to be used with a flow of 2 L/minute additional air or oxygen (to be decided by the Investigator based on oxygen need of the subject).

The formulation of ALX-0171 (and matching placebo) was developed specifically as a liquid solution for inhalation, to ensure rapid delivery of the study drug to the site of RSV infection, and to maintain product quality and stability in combination with the nebulization protocol.

- The formulation buffer is comparable to a normal 0.9% saline solution with respect to salt content but has additional buffering capacity. The osmolality and ion concentration of the (isotonic) solution were chosen to be within the physiological range. The phosphate buffer helps to maintain constant pH, and therefore, to guarantee stability of the drug.
- All excipients comply with the European Pharmacopoeia and the United States Pharmacopoeia.
- The formulation contains no antimicrobial preservatives or tension active agents (surfactants), and no coloring agents, flavors, or sugars/sweeteners are present. Correspondingly, the nebulizer solution does not have a specific taste or odor.

The use of formulation buffer as placebo is considered appropriate, as it is the most representative control for the active study drug, while the minute amounts of phosphate present in the buffer would not be expected to result in effects different from saline. Throughout the clinical studies conducted with ALX-0171 and placebo, there were no consistent findings that would suggest a direct effect of the formulation buffer on respiratory parameters.



Details on initiation, interruptions and completion of study drug administration, will be collected in the electronic case report form (eCRF), as will the acceptability of the face mask and nebulizer and whether or not correct administration was achieved.

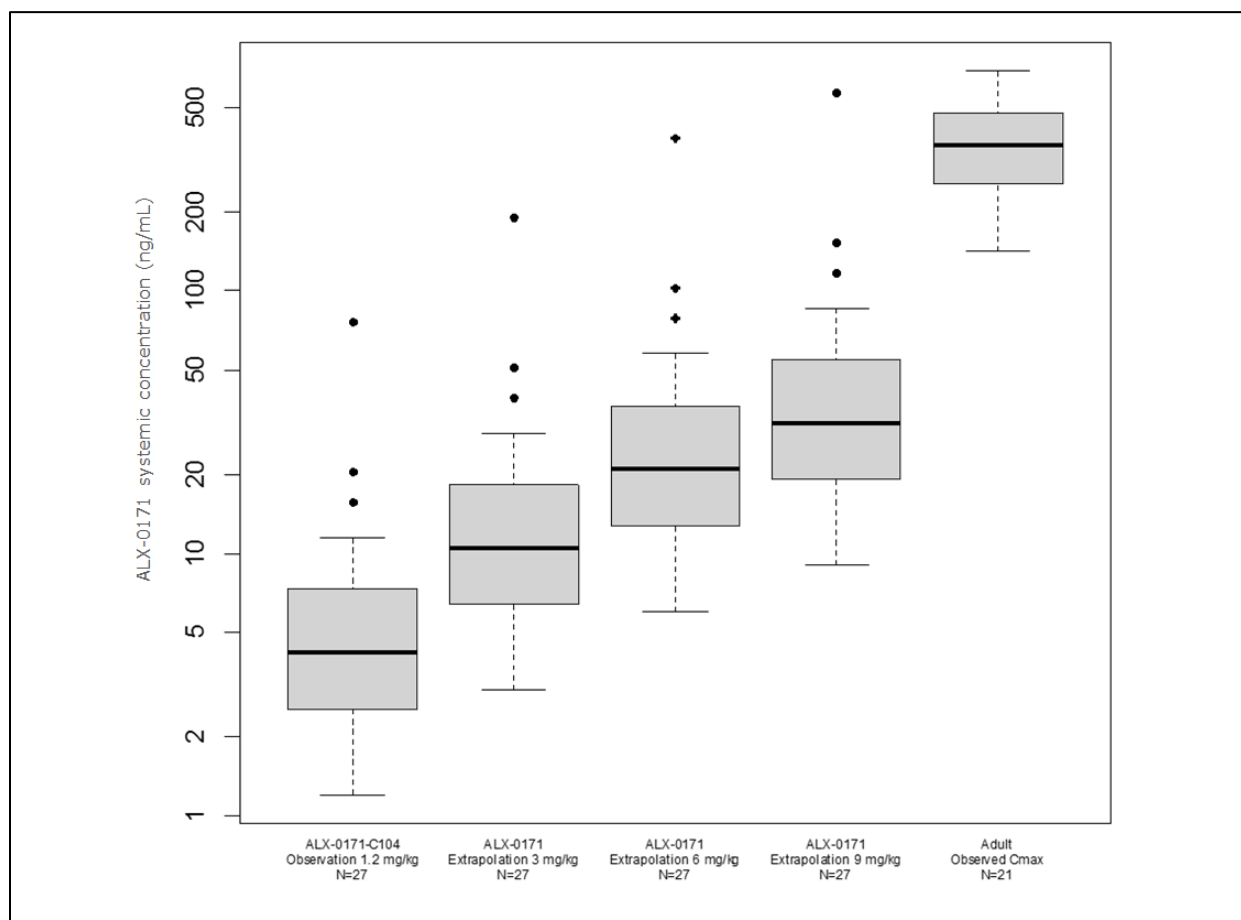
### 3.3.2. SELECTION OF DOSES IN THE STUDY

The dose range proposed to be studied in ALX0171-C203 was selected based on the results of study ALX0171-C104 (Phase 1/2a first-in-infant study), and includes the doses currently being evaluated in ongoing study ALX0171-C201 (Phase 2b dose-range finding study conducted outside of Japan).

- The starting dose for ALX0171-C203 (target average dose: 1.5 mg/kg ALX-0171) is the same as the dose evaluated in the first-in-infant study (target minimal dose 1.2 mg/kg ALX-0171). This dose was selected for the first-in-infant study based on a physiologically based PK (PBPK) model that bridged nonclinical, human adult and human pediatric PK characteristics by taking into account growth and developmental processes such as organ maturation, changes in blood flow, body composition, and ontogeny of elimination mechanisms [24]. In total, 53 infants and young children hospitalized for RSV LRTI were included in study ALX0171-C104. The results indicated that this dose was well tolerated in all age groups (28 days to 24 months). Reductions in nasal viral load (obtained from nasal swab specimens) were noted, confirming that ALX-0171 exhibits antiviral activity when relevant concentrations are achieved.
- As the ALX-0171 serum concentrations measured in the first-in-infant study were below the initial PBPK model predictions, higher doses (mean target doses of 3, 6, and 9 mg/kg ALX-0171) were selected for the subsequent dose-range finding study ALX0171-C201, aiming to attain higher local (lung) concentrations. The dose selection of study ALX0171-C201 was based on data from nonclinical and clinical studies, and maintains adequate safety margin compared to nonclinical and clinical studies (see below). Study ALX0171-C201 is currently ongoing outside of Japan.

The three higher dose levels for study ALX0171-C203 (3.0, 6.0 and 9.0 mg/kg ALX0171) are the same as those evaluated in ALX0171-C201. As shown in [Figure 4](#), the expected plasma concentrations (at 6 hours post-dose) in study ALX0171-C203 (and study ALX0171-C201) do not exceed those measured previously in studies in adults.

**Figure 4: Comparison of observed and extrapolated ALX-0171 plasma concentration in pediatric population with adult observed  $C_{max}$  at 200 mg QD and 105 mg BID repeated dose**



$C_{max}$ =peak plasma concentration; BID=twice a day; QD=once a day.

Boxplots indicating median, upper, and lower quartile. The notches are the estimation of the 95% confidence interval. Black dots are 3 outliers reported in study ALX0171-C104. Y-axis is in logarithmic scale. Only quantifiable values were considered for the ALX0171-C104 study and the extrapolation of higher doses.

The difference between the 1.2 mg/kg dose from the ALX0171-C104 study and the 1.5 mg/kg dose in study ALX0171-C203 is negligible, as the two dose ranges largely overlap. No separate boxplot was included.

Safety margins were calculated based on results obtained in a pivotal toxicity study conducted in Sprague Dawley rats after 14 day repeated administration via inhalation (see IB). Supportive information from (i) a PK study in juvenile rats after single or repeated inhalation, and (ii) a neonatal lamb study after single dose in uninfected animals and after repeated dose in RSV uninfected or RSV-infected animals did not yield unexpected retention of ALX-0171 in tissue or plasma. Concentrations in lung in juvenile rats were somewhat lower when compared to adult rats, with high variability to be considered in the study. No safety signals were detectable in either study in neonatal or juvenile animals. Based on the available information, a correction of calculations based on the GLP-generated data in the toxicity studies was not considered warranted.

- For calculating the safety margins, *in vitro* Sophia anatomical infant nose-throat (SAINT) model data was used to predict the ALX-0171 dose that will come into contact with the infants. The inhaled dose (i.e., the lung dose and the dose deposited in the nasopharyngeal airways) and the dose on the face/oral cavity were taken into consideration and were experimentally shown to be 29.1% of the nebulizer filling dose. This fraction of the nebulizer filling dose is assumed to be totally deposited in the lungs. This was assumed as “maximally expected local exposure”.
- The maximally expected local exposure in pediatric subjects was compared to the highest lung exposure achieved in the pivotal nonclinical toxicity study (the 14-day repeated dose toxicity study after daily administration via inhalation in rats; see IB). In this study, no AEs were observed, so the highest dose administered (117 mg/kg) was considered safe. Assuming 10% lung deposition in rat, the highest local dose achieved was 11.7 mg/kg or 2.3 mg/g lung (female numbers were used as these were lower than males).
- Local safety margins were calculated taking the 29.1% fraction of the nominal dose in the planned clinical study. With a maximal nominal dose of 10.7 mg/kg (see section 3.3.4), and assuming a 1.8% lung weight to body weight ratio [25], the calculated maximal deposited dose is 0.17 mg/g lung in the planned pediatric population.
- The corresponding safety margin was calculated as the ratio between maximal achieved dose in rat (2.3 mg/g lung) to maximal calculated deposited dose in patients (0.17 mg/g lung), which results in a safety margin of  $\geq 13.3$ .

### 3.3.3. IDENTITY OF STUDY DRUG

ALX-0171 and matching placebo will be provided in sterile, preservative-free, masked depyrogenated single-use DIN 2R glass vials, with injection stoppers and aluminium crimped caps. Each vial contains  $\geq 2$  mL nebulizer solution (target fill volume: 2.2 mL).

#### ALX-0171

- Formulation: nebulizer solution
- Route of administration: inhalation (to be administered via the FOX-Flamingo inhalation system)
- Active substance: ALX-0171 Nanobody
- Activity: ALX-0171 Nanobody specifically and potently binds to the RSV F protein, thereby inhibiting an early step in the viral replication cycle.
- Composition: [REDACTED]

### Matching placebo

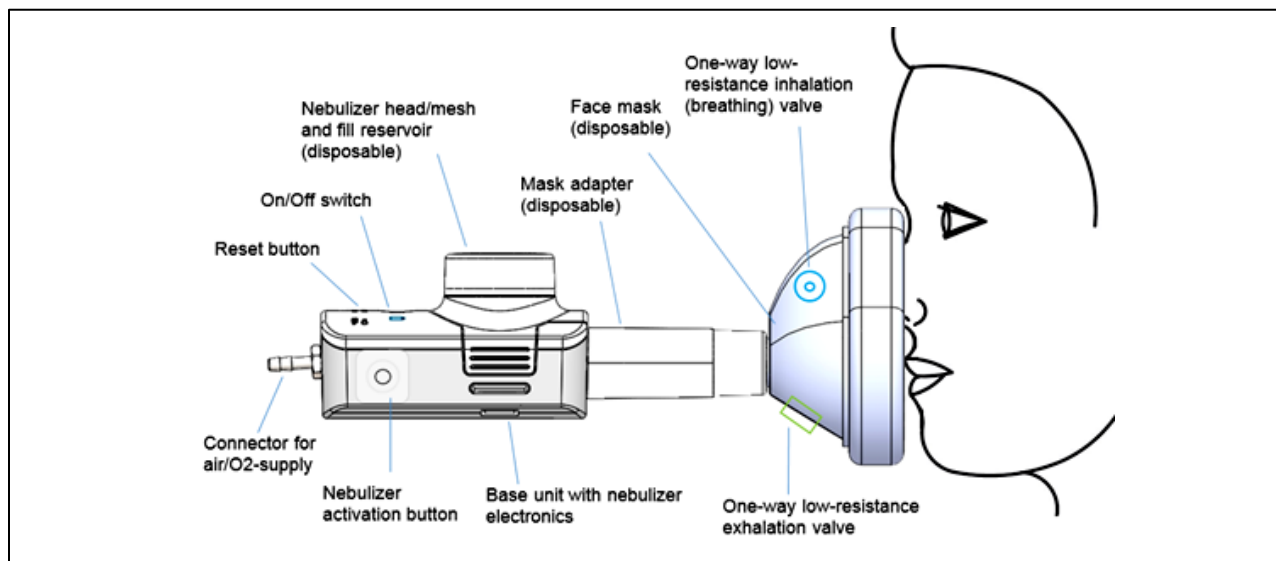
- Formulation: nebulizer solution
- Route of administration: inhalation (to be administered via the FOX-Flamingo inhalation system)
- Active substance: None
- Activity: None
- Composition: [REDACTED]

### Device

- Name: FOX-Flamingo inhalation system - CE marked ([Figure 5](#)).
- Main components: re-usable single-patient base unit (containing the electronics), disposable inhalation set (including pediatric face mask in 2 sizes, mask adapter, vibrating mesh nebulizer reservoir).
- Description: Vibrating mesh type nebulizers are considered the most appropriate technology for nebulization of a therapeutic protein such as ALX-0171 Nanobody. The FOX-Flamingo inhalation system consists of a battery-operated, hand-held device, intended for single-patient use. The device provides an aerosol with particle size suitable for the intended study population. The nebulizer is always to be used with a flow of 2 L/minute additional air or oxygen.

Instructions for preparation, use and handling of study medication, the appropriate volume to be administered and the materials to be used are provided in a manual concerning study drug. Instructions for use for the FOX-Flamingo nebulizer are also provided.

**Figure 5: Overview of the FOX-Flamingo inhalation system**



### 3.3.4. STUDY DRUG ADMINISTRATION

Four doses are planned to be evaluated. The precise dose administered depends on the subject's weight: the drug volume filled into the nebulizer (nominal dose range) is calculated per weight category range (see [Table 1](#)).

- Dose 1: target dose of 1.5 mg/kg (depending on the subject's weight category, the actual nominal dose of 1.5 mg/kg is between 1.3 and 2.0 mg/kg)
- Dose 2: target dose of 3.0 mg/kg (depending on the subject's weight category, the actual nominal dose is between 2.5 and 3.6 mg/kg)
- Dose 3: target dose of 6.0 mg/kg (depending on the subject's weight category, the actual nominal dose is between 5.0 and 7.1 mg/kg)
- Dose 4: target dose of 9.0 mg/kg (depending on the subject's category, the actual nominal dose is between 7.6 and 10.7 mg/kg)

An overview of the appropriate volumes to be filled into the nebulizer, and an indication for minimum and maximum nebulization times, is available in [Table 1](#). The administered dose of ALX-0171 is standardized for body weight categories. This is supported by adequate safety margins (see section [3.3.2](#)), and also takes into account feasibility of accurately measuring and filling the appropriate volume into the nebulizer with a graduated syringe.

The study drug will be administered as a single nebulization. However, due to limitations in the volume that can be filled into the nebulizer, 2 consecutive nebulizations are necessary for the administration of the highest dose (9 mg/kg) in subjects weighing  $\geq 10$  kg.

Study drug administration should start within 3 hours following randomization. Subsequent doses of study drug will be administered at 24-hour intervals ( $\pm 4$  hours) relative to the first dose. No pre-medication is required per protocol, but an inhaled  $\beta_2$ -agonist may be administered at the discretion of the treating Investigator.

**Table 1: Study drug nebulizer filling volumes and nebulization times by dose**

Weight category	Fill volume (and approximate nebulization time)			
	Dose 1 (1.5 mg/kg)	Dose 2 (3 mg/kg)	Dose 3 (6 mg/kg)	Dose 4 (9 mg/kg)
3.0 to <4.0 kg	0.10 mL (~20-40 sec)	0.20 mL (~30-80 sec)	0.40 mL (~65-180 sec)	0.60 mL (~100-290 sec)
4.0 to <5.0 kg	0.15 mL (~25-60 sec)	0.25 mL (~40-105 sec)	0.50 mL (~80-230 sec)	0.75 mL (~130-380 sec)
5.0 to <7.0 kg	0.20 mL (~30-80 sec)	0.35 mL (~55-155 sec)	0.70 mL (~120-350 sec)	1.05 mL (~195-580 sec)
7.0 to <10.0 kg	0.25 mL (~40-105 sec)	0.50 mL (~80-230 sec)	1.00 mL (~180-545 sec)	1.50 mL (~310-930 sec)
10.0 to <12.0 kg	0.35 mL (~55-155 sec)	0.65 mL (~110-320 sec)	1.30 mL (~255-770 sec)	1.50 mL (~310-930 sec) + 0.45 mL (~70-205 sec)
12.0 to <15.0 kg	0.40 mL (~65-180 sec)	0.75 mL (~130-380 sec)	1.50 mL (~310-930 sec)	1.50 mL (~310-930 sec) + 0.75 mL (~130-380 sec)

Note: Indicative values given as minimum and maximum nebulization times.

### **3.3.4.1. ADMINISTRATION PROCEDURE**

The FOX-Flamingo nebulizer features a tubing connector for air or oxygen supply, and is always to be used with a fixed 2 L/minute flow of air, or if needed, oxygen (to be decided by the Investigator based on oxygen need of the subject).

- During administration, the face mask should always be in contact with the face of the subject: a close fit is essential for appropriate dose administration. Hence, administration by "blow by" technique (i.e., hovering the face mask in front of the child during administration) is not permitted.
- At the start of each study drug nebulization, the face mask (connected to the nebulizer) will be placed on the subject's face, and must be verified as being in contact with the face. If applicable, the subject's nasal cannula, face mask, or headbox will need to be removed immediately before administration of the study drug (air or oxygen are provided through the nebulizer). A nasogastric tube, if used, is to remain in place.<sup>\*\*</sup>

<sup>\*\*</sup> Presence of the nasogastric tube has a negligible influence on the inhaled dose of study drug.

- Once the subject is able to breathe comfortably in the face mask, the nebulization procedure should be started.
- Nebulization should proceed as long as aerosol is visible in the transparent face mask.

### **3.3.4.2. ADDITIONAL GUIDANCE**

If dosing cannot be initiated successfully (e.g., because the subject is so agitated as to prevent adequate contact of the face mask with the face, and/or is crying or coughing intensely), new attempts should be made within a maximum of 1 hour (60 minutes) of nebulizer filling.

- If on Day 1, study drug initiation has not been successful after 60 minutes<sup>§§</sup>, the subject will be withdrawn from the study (see section 3.4).
- If on Day 2 or Day 3, study drug initiation<sup>\*\*</sup> has not been successful after 60 minutes, study drug treatment should be discontinued (i.e., in case dose initiation was not successful on Day 2, then no dosing on Day 3 should be done). The subjects should remain in the study and all per protocol visits should be conducted according to the [Schedule of Assessments](#).

The timing of nebulization should be as close to the timeframes specified in the [Schedule of Assessments](#) as possible.

If the nebulization procedure is started successfully but cannot be continued and needs to be interrupted (e.g., because the subject starts crying intensely, or if the face mask loses adequate contact with the subject's face), study drug administration is to be stopped and resumed as soon as possible. Study drug administration should be completed within 2 hours (120 minutes) from nebulizer filling for this nebulization. Subsequent daily study drug administration should continue per protocol.

For subjects weighing  $\geq 10$  kg in the 9 mg/kg dose group, the second of the 2 serial nebulizations should be initiated as soon as possible after the end of the first nebulization and should be completed within 2 hours (120 minutes) from nebulizer filling for this nebulization. In case the study drug administration of the second nebulization was started successfully but could not be completed, appropriate documentation is needed in the medical file and eCRF but subsequent daily study drug administration should continue per protocol.

The exact times of study drug administration (i.e., initiation and end of each nebulization) and number of interruptions, if any, will be recorded in the eCRF. In addition, acceptability of the face mask and the nebulizer after each complete or partial administration, and

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<sup>§§</sup> In case of subjects weighing  $\geq 10$  kg in the 9 mg/kg dose group, this refers to the first of 2 serial nebulizations.

whether or not correct and complete administration could be achieved will be documented in the eCRF.

The product-contacting parts of the nebulizer (i.e., the nebulizer mesh/head and fill reservoir, mask adapter, and face mask) are to be disposed of after each nebulization; only the base unit containing the electronics and the air/oxygen tubing will be reused (per subject and per 3-day treatment window). After completing the study drug treatment period, the base unit of the nebulizer must be safely disposed in a secured environment for further return to the sponsor or designee (e.g., delegated CRO).

### **3.3.4.3. MANAGEMENT OF OVERDOSE**

The intended dose of ALX-0171 should not be exceeded during the study. No antidote is available.

Overdoses that occur during the study should be documented and reported to the Sponsor or designee whether or not it results in an AE/SAE. Overdoses with signs and symptoms need to be reported as an AE/SAE. For information on medication errors, please refer to section [4.2.1](#).

### **3.3.5. DRUG ACCOUNTABILITY**

The Pharmacist, the Investigator or his/her designee is responsible for the acknowledgement of receipt for each shipment of study drug/inhalation system and will verify the condition and quantity of the study drug and other clinical supplies related to Investigational Medicinal Product (IMP) administration.

At study site, the study drug will be kept in a locked and secured storage facility accessible only to those authorized by the Investigator to dispense the study drug.

The responsible person will keep an inventory. This will include the quantity of study drug/inhalation system received for the study and a record of the materials that are dispensed, to whom (subject number) and when.

The pharmacist, the Investigator and/or designated personnel will conduct a final inventory of the study drug/inhalation system and will record the results of this inventory. Upon Sponsor approval, all study drug and clinical supplies will be returned to the depot, or will be destroyed locally according to local regulations and site procedures.

Instructions for drug/inhalation system accountability are available in the manual concerning study drug.



### **3.3.6. STUDY DRUG HANDLING**

Instructions for study drug receipt, handling, storage and administration are available in the manuals concerning study drug and IWRS/IVRS.

#### **Packaging and Labeling**

Final packaging and labeling will comply with the local regulatory requirements. Details on packaging and labeling are provided in the study drug manual.

#### **Storage**

Study drug will be provided under refrigerated conditions and must be stored in a secure, limited-access location protected from light and under the storage conditions specified by the Sponsor.

Study drug must be refrigerated at 2°C to 8°C and should be stored in the secondary packaging until administration. It should not be frozen or shaken.

Site storage conditions should be monitored by the site personnel and reviewed by the monitor during site visits. Deviations from the storage requirements must be documented and reported to the Sponsor, according to the instructions provided in the manual concerning study drug.

#### **Dispensing**

The Investigator or qualified designee(s) will dispense (via IWRS/IVRS) study drug/inhalation system to subjects who have met the entry criteria. Clinical supplies (including study drug) may not be used for any purpose other than that which is stated in this protocol.

#### **Product Quality Complaint**

Product quality complaints have to be communicated (written or electronically) to the Sponsor. Instructions for product quality complaint handling are available in the manual concerning study drug.

For medical device issues see section [4.2.2](#).

### **3.3.7. CONCOMITANT THERAPY**

Any concomitant medication (including over-the-counter medications and herbal supplements) taken during the study (i.e., from signing of the ICF until the subject's last visit), must be recorded in the eCRF. Items to be recorded concerning concomitant medication include: dose and units of dose, start and end date, administration frequency, route of administration, therapeutic indication, brand name (or generic name if brand name is not available). Of note, previous medications relevant for eligibility will also be recorded in the eCRF.

#### **3.3.7.1. STANDARD OF CARE TREATMENT**

The treatment and care provided to each subject are determined by the Investigator (or designee) according to institutional practice. The recommendations on the diagnosis, management, and prevention of bronchiolitis, as described by the American Academy of Pediatrics [1], may be followed in addition to institutional practice.

Treatment may include (but is not limited to) the following:

- Oxygen supplementation through nasal cannula, via face mask or headbox. The initiation, monitoring and weaning of oxygen supplementation will follow local practice. It should be removed for the nebulized study drug administration, during which air or oxygen flow of 2 L/minute is provided
- Fluid/food supplementation (i.v. or via nasogastric tube, if applicable)
- Antipyretics and/or nonsteroidal anti-inflammatory medication
- Inhalation of hypertonic saline (but not within 4 hours before start or 4 hours after the EOS drug administration)
- Short acting  $\beta_2$ -agonists
- Antibiotics (in case of secondary bacterial infection)
- Epinephrine
- Anticholinergics

Apart from those listed under the prohibited medications (see below), concomitant medications are permitted at the Investigator's discretion (based on medical need).

#### **3.3.7.2. PROHIBITED MEDICATIONS**

The following medications are prohibited up to the FU visit (Day 14  $\pm$  2 days):

- Ribavirin, i.v. immunoglobulin and palivizumab Heliox
- Leukotriene receptor antagonists (LTRAs, i.e. montelukast) and/or sodium cromoglycate; initiation of LTRAs and/or sodium cromoglycate is not permitted; infants who are on a maintenance therapy at screening are to continue their usual dose during the study.

- Exogenous surfactant
- Systemic corticosteroids; initiation of inhaled corticosteroids is not permitted; infants who are on a maintenance therapy of inhaled corticosteroids at screening are to continue their usual dose during the study. Of note, topical corticosteroids for the treatment of skin disorders are permitted.
- Mucolytics are permitted until screening but their continuation or initiation during the study is not allowed.

Subjects whose respiratory condition is deteriorating (e.g., hypercapnia with  $p\text{CO}_2 > 8$  kPa/60 mmHg, decreased consciousness) and need to start non-invasive respiratory support or invasive ventilation need to discontinue study drug treatment but should remain in the study according to the in-hospital post-treatment period as specified in the [Schedule of Assessments](#), and should also attend the FU and EOS visits.

Subjects on HFOT as standard of care at inclusion and for whom the flow needs to be increased to levels not enabling study drug nebulization and/or above 2 L/kg/minute also need to discontinue study drug treatment and be further followed up as described above. SAE reporting is required for these subjects with deterioration of the respiratory condition requiring above mentioned methods of ventilation.

After the end of the subject's participation in the study, each subject is to be treated according to standard clinical practice.

### **3.3.8. TREATMENT COMPLIANCE**

Study drug will be administered by a health care professional in hospital, ensuring treatment compliance.

The exact times of study drug administration (i.e., initiation and end of each nebulization and number of interruptions, if any) will be recorded in the eCRF. In addition, acceptability of the face mask and the nebulizer after each complete or partial administration, and whether or not correct and complete administration could be achieved will be documented in the eCRF. Compliance will be further confirmed by bioanalytical assessment of ALX-0171 in blood samples, and could be further confirmed by electronic documentation of the administration on the nebulizer base unit.

## **3.4. WITHDRAWAL AND DISCONTINUATION CRITERIA**

### **3.4.1. WITHDRAWAL FROM THE STUDY**

Every reasonable attempt should be made by the Investigator (or his/her designee) to keep subjects in the study, however, a subject must be withdrawn from the study if:

- Study drug administration cannot be successfully initiated on Day 1 (see section 3.3.4.2).
- The Investigator considers it, for safety reasons, in the best interest of the subject.
- The parent(s)/legal guardian(s) withdraw(s) consent.

A subject may be withdrawn from the study if the subject and/or parent(s)/legal guardian(s) fail to comply with dosing, evaluations, or other requirements of the study.

In case a subject is withdrawn from the study for any reason other than death, lost to follow-up or informed consent withdrawal (including subjects randomized but not dosed), a Withdrawal visit should be conducted at the time of withdrawal.

The reason for withdrawal should be recorded in the eCRF. Investigators (or their designees) must attempt to contact the parent(s) or legal guardian(s) of subjects who fail to attend scheduled visits by telephone or other means, to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed-up as described in section 4.

If a subject is withdrawn from the study, the study monitor and the Sponsor are to be informed immediately.

### **3.4.2. DISCONTINUATION OF STUDY DRUG**

A subject must be discontinued from study drug treatment if:

- The randomization code is broken prematurely by the Investigator or Sub-Investigator.
- A severe and/or serious hypersensitivity reaction to study drug occurs.
- A severe and/or serious acute respiratory distress reaction induced by study drug administration occurs.
- The subject needs to start treatment with one of the medications listed as prohibited (see section 3.3.7).
- The subject needs to start non-invasive respiratory support, invasive ventilation or HFOT at levels not enabling removal of the cannula for administration of the study drug nebulization and/or levels exceeding 2 L/kg/min. The event will be captured as an SAE and will be monitored until resolution, as described in section 4.1.4.

- If the Investigator or the Sponsor / medical monitor deems it is in the subject's best interest.
- If on Day 2 or Day 3, study drug initiation\*\*\* has not been successful after 60 minutes, study drug treatment should be discontinued (i.e., in case dose initiation was not successful on Day 2, then no dosing on Day 3 should be done).

A subject may be discontinued from study drug treatment if an SAE occurs (if considered necessary or appropriate by the Investigator).

For subjects remaining hospitalized after study drug treatment discontinuation, in-hospital post-treatment assessments will be performed in addition as specified in the [Schedule of Assessments](#). Subjects who discontinued treatment prematurely (for any reason) should also attend the FU and EOS visits.

If a subject is discontinued from the study drug, the study monitor and the Sponsor are to be informed immediately.

### **3.5. STUDY TERMINATION**

If the Sponsor decides not to start the study prior to commencement of any protocol activities, and/or after Institutional Review Board (IRB) approval have been received, the Investigator or Sponsor must notify the IRB by letter outlining the reasons for abandonment of the study, as required per national regulations.

At any time during the study, the Sponsor may suspend or terminate the study or part of the study for any reason. If the Investigator plans to suspend or terminate participation in the study, the Investigator will promptly inform the Sponsor and the IRB and provide them with a detailed written explanation.

Upon study completion, the Sponsor will provide the Investigator, IRB with final reports and summaries as required by regulations.

In case of suspension or halt due to safety reasons, the IRB will be notified immediately and at the latest within the number of days as specified by local regulations after the study is halted, clearly explaining the reasons, and describing follow-up measures, if any, taken for safety reasons.

The IDMC, consisting of an independent group of clinical experts will review the available cumulative safety data (i.e., all data from prior visits of all subjects including preceding cohorts). The IDMC will advise the sponsor concerning continuation, modification or potential early termination of the study after every meeting (also see section [3.1.1](#)).

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\*\*\* In case of subjects weighing  $\geq 10$  kg in the 9 mg/kg dose group, this refers to the first of 2 serial nebulizations.

## **3.6. STUDY ASSESSMENTS**

### **3.6.1. TIMING OF ASSESSMENTS**

#### **3.6.1.1. ELIGIBILITY PROCEDURES**

Study related procedures will be done after informed consent has been obtained, after which each subject will be assigned his/her unique subject identification (ID) number. The date of obtaining written informed consent will be recorded in the eCRF. AEs will be recorded from time of obtaining written informed consent to the subject's last visit.

A signed and dated ICF must be obtained from the parent(s)/legal guardian(s) or legally acceptable representative(s) before any study-specific procedures are performed.

The screening process begins when written informed consent has been obtained and continues until randomization. Subjects must be randomized within 24 hours of arrival at the hospital/emergency unit.

#### **3.6.1.2. SCREENING**

Screening assessments and procedures should take place within 24 hours prior to randomization and as specified in the [Schedule of Assessments](#).

Screening procedures/measurements include:

- Informed consent
- Inclusion/exclusion criteria
- RSV diagnosis
- 12-lead ECG
- Demographics and medical history
- Previous and concomitant medications
- Physical examination
- Body weight, height and temperature
- Heart rate and SpO<sub>2</sub>
- Feeding, general appearance, lung auscultation, respiratory muscle retractions, respiratory rate, daytime coughing, night-time coughing,
- Hospitalization information: ICU transfer, apnea episodes, ventilation information, discharge from ICU/hospital
- Parent(s)/caregiver(s) assessment by completion of a diary including scoring of respiratory symptoms and assessing the global condition of the subject
- Blood sample for clinical laboratory
- Blood sample for immunogenicity (ADA)

Data of all subjects screened will be collected in the eCRF in order to assess the numbers and demographic characteristics of the excluded subjects, and the reasons for their exclusion, including documentation of AEs. In case an SAE occurs, this needs to be reported according to standard process (see section 4.1.4).

The results of the screening procedures needed to evaluate eligibility must be available prior to randomization.

### **3.6.1.3. RANDOMIZATION**

After obtaining written informed consent from the parent(s)/legal guardian(s) or legally acceptable representative(s) and screening procedures, eligible subjects will be randomized to the different treatment groups. Randomization should take place within 24 hours from arrival at the hospital/emergency unit.

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 and dosing, unless these assessments were already performed within the last 3 hours before randomization.

At screening, subjects will receive a unique ID number, assigned by IWRS/IVRS. At randomization, subjects will be assigned a randomization number by IWRS/IVRS prior to study drug administration according to the randomization scheme.

Sequential dose escalation will be used to enable appropriate safety follow-up. Each of the 4 cohorts will consist of 15 subjects randomized and treated in a 4:1 ratio to receive either ALX-0171 or placebo (N=12 active versus N=3 placebo per cohort). After each cohort (the last subject in the cohort has completed the treatment period), an IDMC will review the available cumulative safety data and advise the Sponsor on proceeding to the subsequent cohort (i.e., the next higher dose).

### **3.6.1.4. STUDY DRUG TREATMENT PERIOD**

During the study drug treatment period, assessments should be performed as specified in the [Schedule of Assessments](#).

If screening assessments are performed within 3 hours before the first dose on Day 1, the Day 1 pre-dose assessments do not need to be repeated; only the remaining assessments planned on Day 1 (pre-dose) will need to be performed.

Subjects will receive once-daily administration of study drug on 3 consecutive days. The first dose of study drug is to be administered as soon as possible and within 3 hours after randomization. Study drug administration should take place within 24 hour intervals ( $\pm 4$  hours) relative to the start of the first nebulization of the first dose. For subjects requiring 2 serial nebulizations (subjects weighing  $\geq 10$  kg in the 9 mg/kg dose group), the timing of study drug administrations should be relative to the start of their first nebulization.

For all subjects, the exact date, start and end time (and number of interruptions, if any) of the study drug nebulizations will be collected in the eCRF.

Hospitalization information will be collected throughout the study, including 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 as well as adequate stable oxygen saturation on room air of  $\geq 95\%$  for at least 4 hours to enable discharge. In case of oxygen supplementation, the level of supplementation is to be considered for reduction at least three times per day. Provided oxygen saturation is stable, attempts to remove the supplementation will be done at least three times a day.

After the 3 days of treatment and provided that the clinical response criteria have been met (which are based on adequate oral feeding and oxygen saturation), discharge from the hospital can take place per protocol at the Investigator's discretion from dosing on Day 3 onwards (after all required post-dose assessments have been completed).

### ***3.6.1.5. IN-HOSPITAL POST-TREATMENT PERIOD***

Subjects who are not discharged from the hospital after completion of the treatment period or subjects remaining hospitalized after study drug treatment discontinuation will enter an in-hospital post-treatment period with assessments in the morning and evening until discharged.

All assessments will be performed as specified in the [Schedule of Assessments](#).

For subjects in the in-hospital post-treatment period, the mid-turbinate nasal swab should be collected only on the day of hospital discharge.

### ***3.6.1.6. WITHDRAWAL VISIT***

In case a subject is withdrawn from the study for any reason other than death, lost to follow-up or informed consent withdrawal (including subjects randomized but not dosed), a Withdrawal visit should be conducted at the time of withdrawal. The reason for withdrawal should be recorded in the eCRF.



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.

### ***3.6.1.7. FOLLOW-UP AND END-OF-STUDY VISITS***

Subjects who have received at least one dose of study medication should complete a FU visit on Day 14 ( $\pm 2$  days), and an EOS visit on Day 28 ( $\pm 2$  days). After the end of the subject's participation in the study, each subject is to be treated according to standard clinical practice.

### ***3.6.1.8. UNSCHEDULED VISITS***

Unscheduled visits may be conducted to assess and follow-up on AEs or laboratory abnormalities. In such cases, the evaluations performed are at the discretion of the Investigator. Findings during these Unscheduled visits should be reported in the designated sections of the eCRF.

In case a subject is re-hospitalized, or when the Investigator is consulted for a respiratory condition occurring after discharge from the hospital (up to the EOS [Day 28] visit), an Unscheduled Visit is to be performed. In such cases, a mid-turbinate nasal swab is to be collected and a physical examination, including lung auscultation, must be performed.

### ***3.6.1.9. MISSED VISITS***

If a subject misses a study visit for any reason, the Medical Monitor should be contacted as soon as possible to discuss rescheduling options of the missed visit to be proposed to the subject's parent(s)/legal guardian(s). For subjects who are considered lost to follow-up, reasonable attempts must be made (and documented) to obtain information on the subject.

## **3.6.2. BASELINE CHARACTERISTICS**

Demographic and medical history data (including RSV-related signs and symptoms) will be collected at screening.

Collected data will include (but are not limited to): month and year of birth, age (with indication of week), gender, race and ethnicity.

Data on atopy in the family, environmental exposure to tobacco, pets and breastfeeding will also be collected.

The mid-turbinate nasal swab sample collected pre-dose on Day 1 will be used to test for concurrent viruses and the presence of mycoplasma at baseline.

### 3.6.3. SAFETY ASSESSMENTS

The safety and tolerability profile of ALX-0171 will be collectively assessed with the following outcome measures:

- TEAEs as noted by healthcare staff and/or reported by parents/caregivers. The Investigator (or his/her designee) will review at each visit whether AEs/SAEs have occurred since the last visit.
- Heart rate, respiratory rate (measured over a 1-minute interval) and SpO<sub>2</sub>.
- Body temperature and body weight.
- Physical examination including the skin, ears/nose/throat, heart auscultation, lung auscultation, and abdomen.
- Clinical laboratory test results

At each of the time points indicated in the [Schedule of Assessments](#), a physical examination should be performed, including heart auscultation, examination of abdomen, skin and ears/nose/throat. Lung auscultation is to be performed more frequently and is therefore listed separately in the [Schedule of Assessments](#).

The parent(s)/legal guardian(s) will receive a subject card, indicating the address and phone number of the Investigator and/or other relevant emergency contact details (including e.g., subject number, medication number). The subject's parent(s)/legal guardian(s) will be advised to carry this card with them throughout the study so that the appropriate actions can be undertaken in case of emergency. They will also be advised to contact the Investigator (or his/her designee) with any medical and/or safety concern.

In order to appropriately document possible events after discharge from the hospital, a diary will be completed by the parent(s) or caregiver(s) and be brought to the site at the FU visit on Day 14 and EOS visit on Day 28.

#### 3.6.3.1. ADVERSE EVENTS

Definitions and general information on evaluation and reporting of AEs/SAEs and adverse drug reactions are provided in section 4.

#### 3.6.3.2. HEART RATE AND SPO<sub>2</sub>

Continuous monitoring of SpO<sub>2</sub> needs to be done during the study drug treatment period and the in-hospital post-treatment period until the clinical response criterion for oxygen

saturation on room air ( $\text{SpO}_2 \geq 95\%$  for at least 4 hours) has been met and/or in case saturation monitoring is to be continued according to the Investigator's judgment.

The values for these parameters will be regularly captured in the eCRF (together with e.g., oxygen flow delivered and method), according to the [Schedule of Assessments](#). In addition, the date and time of achieving the clinical response criterion for oxygen will be collected in the eCRF (CFR clinical response information collection).

Clinically significant changes from baseline (warnings and measurements) during the pulse oximetry monitoring period are to be captured as AEs in the eCRF.

Evolution of the heart rate and oxygen saturation levels can also inform on clinical activity outcome.

### **3.6.3.3. CLINICAL LABORATORY ASSESSMENTS**

Blood samples for clinical laboratory analyses will be collected at the time points indicated in the [Schedule of Assessments](#).

Safety laboratory assessments are planned two times during the study (at screening and at the FU/Withdrawal visit) and will be performed by the local laboratory in order to allow timely availability of the results. For local laboratory data, the local normal ranges and laboratory accreditation must be collected/provided.

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.

The blood samples will be collected according to the site's standard practice. Anesthetic cream or spray can be used to minimize the subject's discomfort and distress.

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

- Clinical chemistry: 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, eosinophils).

Clinical relevance of values outside the local laboratory's normal range will be assessed by the Investigator. All clinically significant laboratory findings will be recorded as AEs in the eCRF.

In the event of unexplained or unexpected clinical laboratory test values, the test(s) may be repeated and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found.

### **3.6.3.4. LUNG AUSCULTATION**

At each of the time points indicated in the [Schedule of Assessments](#), a lung auscultation will be performed to assess wheezing (assessed during expiration/inspiration, lung fields affected), crackles/crepitation and other abnormalities.

A new finding or a change of a finding that is judged as an undesirable medical event shall be reported as an AE.

In case a subject is re-hospitalized, or when the Investigator is consulted for a respiratory condition occurring after discharge from the hospital, an Unscheduled Visit is to be performed. In such cases, a mid-turbinate nasal swab is to be collected and a physical examination, including lung auscultation, must be performed.

### **3.6.3.5. BODY WEIGHT, HEIGHT, AND TEMPERATURE**

At the time points indicated in the [Schedule of Assessments](#), the following parameters will be assessed: body height, body weight, and temperature.

To obtain the actual body weight, subjects must be weighed lightly clothed.

Temperature is to be measured preferably rectal, oral, or tympanic (axillary method less preferred). For each individual subject, the same method should be used throughout the study, if possible. The method will be recorded in the eCRF.

### **3.6.3.6. PHYSICAL EXAMINATION**

At each of the time points indicated in the [Schedule of Assessments](#), a physical examination should be performed, including heart auscultation, examination of abdomen, skin and ears/nose/throat.

Physical examination will be recorded as "normal", "abnormal, not clinically significant" or "abnormal, clinically significant" at every assessment. A new finding or a change of a finding that is judged as an undesirable medical event (including all findings recorded as "abnormal, clinically significant") shall be reported as an AE.

In case a subject is re-hospitalized, or when the Investigator is consulted for a respiratory condition occurring after discharge from the hospital, an Unscheduled Visit is to be performed. In such cases, a mid-turbinate nasal swab is to be collected and a physical examination, including lung auscultation, must be performed.

### **3.6.3.7. ABNORMAL FINDINGS**

Criteria for determining whether an abnormal objective test finding (e.g., laboratory result), a complication of a protocol mandated procedure (e.g., blood draw), or a change in physical examination findings should be reported as an AE include (see section 4), but are not limited to:

1. Result/finding is associated with accompanying clinical signs and symptoms (new onset or aggravated in severity of frequency from baseline condition), and/or
2. Result/finding requires extra diagnostic testing (other than diagnostic exclusion tests) or medical/surgical intervention, and/or
3. Result/finding would require a premature discontinuation from the study drug, significant additional concomitant drug treatment or other therapy, and/or
4. Result/finding leads to any of the outcomes included in the definition of an SAE, and/or
5. Result/finding is considered to be an AE by the Investigator.

Any abnormal test result that is determined to be an error and merely repeating an abnormal test does not require reporting as an AE.

### **3.6.3.8. AIRWAY HYPERRESPONSIVENESS AND HYPERSENSITIVITY**

Airway hyperresponsiveness and immediate or delayed adverse drug reactions should be managed according to the Investigator's clinical judgment and applicable standard of care.

- If airway hyperresponsiveness would occur, administration of a bronchodilator like the short-acting  $\beta_2$ -agonist salbutamol may be administered (with an appropriate follow-up period) according to the Investigator's assessment of the particular reaction and subject's characteristics.
- With regard to immediate or delayed hypersensitivity reactions, measures beyond basic supportive care are not considered necessary for subjects with purely local reactions. Subjects with suspected systemic hypersensitivity, however, should be admitted or treated and observed for a longer period, preferably in the emergency department or another close-observation area, depending on the severity of the reaction and its hemodynamic impact.

In case of severe and/or serious hypersensitivity reactions judged to be related to study drug occurs, an additional serum sample should be collected (if reasonably feasible) as soon

as possible after the start of the event (blood volume: 1 mL) to characterize the reaction (if deemed required). As described in section 3.4, subjects must be discontinued from study drug treatment in case of a severe and/or serious hypersensitivity reaction, a severe and/or serious acute respiratory distress reaction induced by study drug, or when a subject needs to start non-invasive respiratory support or ventilation.

### 3.6.4. PHARMACOKINETIC ASSESSMENTS

Systemic (serum) concentrations of ALX-0171 will be used as a surrogate for local (lung) concentrations.

A total of 3 blood samples for PK analysis are planned to be taken from each subject at the time points specified in the [Schedule of Assessments](#).

- pre-second dose,
- between 0.5 hours and 3 hours after completion of the second dose and at least 1 hour apart from the first sampling, and
- between 3 hours and 6 hours after completion of the second dose and at least 1 hour apart from the previous sampling.

Blood samples for PK analysis do not need to be collected in case study drug was not administered on Day 1 and/or Day 2.

The exact dates and times of blood sampling must be recorded.

If sufficient serum remains after PK assessment, exploratory biomarker (KL-6) may also be evaluated.

The blood samples will be collected from a vein, as using capillary blood (e.g., from heel pricks) is not allowed for PK assessments. Anesthetic cream or spray can be used to minimize the subject's discomfort and distress. For further details on sample collection, shipment, storage and processing, please refer to a separate Laboratory Manual.

Determination of ALX-0171 concentrations in serum will be done by a validated Ligand Binding Assay (LBA)-based method at a designated analytical laboratory according to the bioanalytical methodology and procedures described in a separate Bioanalytical Analysis Plan.

### 3.6.5. ANTIVIRAL EFFECT ASSESSMENTS

Throughout the study, nasal swabs (mid-turbinate specimen) will be collected for analysis of viral load (RSV) according to the time points defined in the [Schedule of Assessments](#).

The mid-turbinate nasal swab sample collected pre-dose on Day 1 will also be used to test for concurrent viruses and the presence of mycoplasma at baseline. Confirmation of RSV diagnosis will also be performed at an analytical laboratory using a qPCR assay.

The swabs that will be used are anatomically-designed for the collection of respiratory specimens which allows improved patient comfort and efficiency in specimen collection. In addition, appropriate training on the nasal swabbing procedure will be provided to the clinical sites to enable standardization across the study. Collection of nasal swab samples from both nostrils is preferred.

For all subjects, the exact date and time of nasal swab sampling will be collected in the eCRF.

Note that a mid-turbinate nasal swab should also be taken in case the subject is re-hospitalized or when the Investigator is consulted for a respiratory condition after hospital discharge up to the EOS (Day 28) visit. This should be considered for AE reporting according to the Investigator's judgment; however in any case, in addition to the nasal swab, a lung auscultation and a physical examination should be performed when a subject returns to the hospital or the Investigator is consulted for a respiratory problem. The information on health care utilization for a respiratory condition will be collected through the diary completed by the parent(s)/caregiver(s).

The viral load will be measured by plaque and qPCR assay. Determination of Log<sub>10</sub> plaque forming units (PFU)/mL and Log<sub>10</sub> viral copies/mL in nasal swabs will be done by validated methods at a designated analytical laboratory. Bioanalytical procedures will be described in a separate Bioanalytical Analysis plan.

In order to identify the emergence of resistance towards ALX-0171, the virological samples from ALX-0171-treated patients who fail to respond to therapy or experience viral rebound will be selected and characterized. For these samples, the pre-treatment (baseline) sample and the relevant post-treatment sample will be used for genotypic and phenotypic characterization, to identify mutations that could contribute to reduced susceptibility to ALX-0171.

If permitted by local regulations and only with written informed consent by the subject's parent(s)/legal guardian(s) or the legally acceptable representative(s), nasal swab samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work in the context of the development of ALX-0171.

All nasal samples, including those for exploratory work in the context of the development of ALX-0171 (if applicable), will be kept for up to 5 years after the end of the study. No human DNA or RNA analysis will be performed.

### 3.6.6. CLINICAL ACTIVITY ASSESSMENTS

The following assessments will provide valuable information to evaluate clinical activity of ALX-0171 (in addition to safety):

- Heart rate, respiratory rate (measured over a 1-minute interval) and SpO<sub>2</sub>.
- Feeding: type of feeding support, and (time and date of) sufficient feeding to allow for hospital discharge, in the opinion of the Investigator (with particular attention to hydration and breathing comfort during feeding)
- Wheezing as assessed during lung auscultation
- Cough during the night and during the day
- Respiratory muscle retractions (supraclavicular, intercostal, and subcostal)
- General appearance: activity, irritation, and responsiveness
- Body temperature and body weight
- Occurrence of apnea episodes

Note: Occurrence of episodes of apnea will be captured together with the overall hospitalization information and should be reported as an AE (see section 4). As defined by the American Academy of Pediatrics [1], apnea is “an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia.”

The following medical interventions will also be evaluated:

- Length of hospital stay for RSV infection
- Level, method, and duration of supplemental oxygen therapy
- Initiation of invasive or non-invasive ventilation (i.e., continuous positive airway pressure [cPAP] or HFOT)
- Level, method and duration of invasive or non-invasive ventilation
- Transfer to an ICU and duration of stay in ICU

The clinical activity assessments will be used to calculate the following composite scores (see also section 5.7):

- RDAI score ([Appendix 1](#))
- RACS ([Appendix 1](#))
- Global Severity Score ([Appendix 2](#))
- Time-to-Clinical Response



### 3.6.7. PARENT/CAREGIVER ASSESSMENTS

Parent(s)/Caregiver(s) assessment of the clinical condition of the subject will be done by daily completion of a diary during the hospital stay and up to the EOS (Day 28) visit. The diary will be used to measure three respiratory symptoms (cough, [audible] wheeze, and trouble breathing), to score the general health of the subject and will ask for use of health care utilization and medication for respiratory symptoms.

The three respiratory symptoms (cough, trouble breathing and wheezing) will be scored from not present over very mild, mild, moderate, and severe up to very severe.

The global rating of the child's health by the parent(s)/caregiver(s) will be captured by a VAS. The parent or caregiver will make a mark between 0 ("very bad") and 100 mm ("perfect") on the scale to indicate the subject's current health. In addition, the parent(s)/caregiver(s) will indicate when the child was back to his/her condition as before the RSV infection started.

### 3.6.8. IMMUNOGENICITY ASSESSMENTS

Immunogenicity will be assessed by the presence of pre-Ab, TE ADA, and neutralizing anti-drug antibodies (NAb) in serum.

To assess systemic immunogenicity of ALX-0171, blood samples will be collected at the time points defined in the [Schedule of Assessments](#). If ADA are present, further testing of their neutralizing capacity must be performed.

In case no sample was taken at the screening visit, a blood sample for assessment of immunogenicity should be collected at the Day 1 pre-dose timepoint, if possible. In case no sample was taken at the FU (Day 14) visit, a blood sample for assessment of immunogenicity should be collected at the EOS (Day 28) visit, if possible.

The exact date and time of blood sampling will be recorded.

The blood samples will be collected from a vein, as using capillary blood (e.g., from heel pricks) is not allowed for ADA assessments. Anesthetic cream or spray can be used to minimize the subject's discomfort and distress. For further details on sample collection, shipment, storage and processing, please refer to a separate Laboratory Manual.

Of note, an additional serum sample should be collected (if reasonably feasible) in case a serious and/or severe hypersensitivity reaction judged to be related to study drug occurs. The sample (blood volume: 1 mL) should be collected as soon as possible after the start of the event to allow characterization of the reaction if deemed required (also see section [3.6.3.8](#)).

Determination of ADA will be done using a validated screening, confirmation and titration ADA bridging assay, with further characterization of ADA positive samples by a competitive ligand binding neutralizing antibody assay. The immunogenicity data will be processed according to a dedicated Bioanalytical Analysis plan.

Bioanalytical procedures for the additional sample in case of serious and/or severe hypersensitivity reaction will be described in a separate Bioanalytical Analysis plan.

### **3.6.9. PHARMACODYNAMIC ASSESSMENTS**

PD measurements will include the quantification of the biomarker Krebs von den Lungen-6 (KL-6) levels in serum. KL-6 will be assessed on the remainder (if any) of the blood samples obtained for PK or immunogenicity testing, once the appropriate volume for their intended purpose has been extracted.

Exploratory analysis of KL-6 levels will be done according to the time points defined in the [Schedule of Assessments](#).

Determination of KL-6 levels in serum will be done by validated methods at the Sponsor. Bioanalytical procedures will be described in a separate Bioanalytical Analysis plan.

### **3.6.10. TOTAL BLOOD VOLUME**

Blood samples collected in this study will be used:

- i) for safety evaluation (clinical laboratory: hematology and clinical biochemistry),
- ii) to monitor the systemic concentration of ALX-0171 (as a surrogate measure of the local lung concentration), and
- iii) to assess potential immunogenicity ([Table 2](#)).

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.

The blood samples for PK or ADA assessments will be collected from a vein, as using capillary blood (e.g., from heel pricks) is not allowed.

The precise assessments that are intended to be performed on each of the blood samples are arranged by priority; when insufficient volume is available (e.g., because of difficulties in or limits to obtaining blood), only the highest priority (-ies) will be assessed (see [Table 2](#)).

**Ablynx NV****Clinical Study Protocol ALX0171-C203****Final Version 3.0****Table 2: Timing, priority and estimated volume of scheduled blood draws**

Sample	Priority	Maximal Target volume
1 blood draw at screening <sup>a</sup>	1. Clinical laboratory: <ul style="list-style-type: none"> <li>- Hematology (whole blood)</li> <li>- Biochemistry (serum)</li> </ul> 2. Immunogenicity (serum) <sup>b</sup> 3. Exploratory biomarker <sup>c</sup>	<ul style="list-style-type: none"> <li>- whole blood for hematology (volume according to local practice)</li> <li>- whole blood to be processed into serum for biochemistry (volume according to local practice)</li> <li>- 1 mL whole blood, to be processed into serum for immunogenicity and biomarker <sup>b</sup></li> </ul> <b>Total: 1 mL whole blood + volume needed for clinical laboratory</b>
3 blood draws on Days 2-3	1. PK (serum) 2. Exploratory biomarker <sup>b</sup>	<ul style="list-style-type: none"> <li>- 0.5 mL whole blood, to be processed into serum for PK and biomarker <sup>b</sup></li> </ul> <b>Total: 1.5 mL whole blood</b>
1 blood draw during the Day 14 FU visit	1. Clinical laboratory: <ul style="list-style-type: none"> <li>- Hematology (whole blood)</li> <li>- Biochemistry (serum)</li> </ul> 2. Immunogenicity (serum) <sup>b</sup> 3. Exploratory biomarker <sup>c</sup>	<ul style="list-style-type: none"> <li>- whole blood for hematology (volume according to local practice)</li> <li>- whole blood to be processed into serum for biochemistry (volume according to local practice)</li> <li>- 1 mL whole blood, to be processed into serum for immunogenicity and biomarker <sup>b</sup></li> </ul> <b>Total: 1 mL whole blood + volume needed for clinical laboratory</b>

<sup>a</sup> 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.

<sup>b</sup> For subjects with a body weight below 5 kg and in case the blood volume needed for local clinical laboratory exceeds 2.5 mL, the sample for analysis of immunogenicity should not be collected at screening and on Day 14, but on Day 1 pre-dose and on Day 28, if possible.

<sup>c</sup> Only if sufficient blood volume (serum) is available after analyzing the samples obtained for PK or immunogenicity.

Exploratory biomarker will only be assessed on the remainder of the blood samples once the appropriate volume for their intended purpose has been extracted. Note that no human DNA or RNA analysis will be performed.

An additional serum sample should be collected (if reasonably feasible) in case a serious and/or severe hypersensitivity reaction judged to be related to study drug occurs (blood volume: 1 mL).

Of note: For subjects with a body weight below 5 kg and in case the blood volume needed for local clinical laboratory exceeds 2.5 mL, the sample for analysis of immunogenicity should not be collected at screening and on Day 14, but on Day 1 pre-dose and on Day 28, if possible.

If permitted by local regulations and only with written informed consent by the subject's parent(s)/legal guardian(s) or the legally acceptable representative(s), blood samples that remain after protocol-specific assessments have been performed may be used by the Sponsor for further exploratory work in the context of the development of ALX-0171.

All blood samples, including those for exploratory work in the context of the development of ALX-0171 (if applicable), will be kept for up to 5 years after the end of the study. No human DNA or RNA analysis will be performed.

### **3.6.11. APPROPRIATENESS AND TIMING OF MEASUREMENTS**

The assessments which will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

The timing of all assessments is detailed in the [Schedule of Assessments](#).

Throughout the study, study personnel should make every reasonable effort to follow the timing of assessments and procedures in the [Schedule of Assessments](#) for each subject.

## 4. ADVERSE EVENT EVALUATION AND REPORTING

### 4.1. ADVERSE EVENTS

#### 4.1.1. DEFINITIONS

Term	Definition
<b>Adverse Event (AE)</b>	<p>Any untoward medical occurrence in a subject or clinical investigation in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>Other examples include any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.</p> <p>In differentiating between medical history and AEs, the following points will be considered:</p> <ul style="list-style-type: none"><li>• Conditions that started before signing of informed consent and for which no symptoms or treatment are present up to the timing of signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).</li><li>• Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, but with unchanged severity, are recorded as medical history (e.g., allergic pollinosis).</li><li>• Conditions that started or deteriorated after signing of informed consent will be documented as AEs.</li></ul>
<b>Treatment-emergent AEs and SAEs</b>	<p>TEAEs or treatment-emergent SAEs are events temporally associated with the use of study drug (occurring during or after the first dose of study drug), whether considered related to the study drug or not.</p>

Term	Definition
<b>Adverse Reaction</b>	<p>An untoward and unintended response in a subject to an IMP, which is related to any dose, administered to that subject.</p> <p>The phrase "response to an IMP" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.</p>
<b>Serious Adverse Events (SAEs)</b>	<p>An SAE is any untoward medical occurrence (an AE) occurring at any dose of the (investigational) medicinal product, comparator or placebo that fulfils one or more of the following conditions:</p> <ul style="list-style-type: none"> <li>• <b>Results in death</b></li> <li>• <b>Is life-threatening</b></li> </ul> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p> <ul style="list-style-type: none"> <li>• <b>Requires inpatient hospitalization or prolongation of existing hospitalization.</b></li> </ul> <p>NOTE: An AE associated with a hospitalization or prolongation of hospitalization will not be regarded as an SAE, if at least one of the following exceptions is met:</p> <ul style="list-style-type: none"> <li>- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition</li> <li>- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g., pre-planned prior to the start of the study hip replacement operation which does not lead to further complications.</li> <li>- Hospital stay of less than 12 hours.</li> <li>- The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).</li> <li>- Any admission to hospital or other institution for general care where there was no deterioration in condition.</li> <li>- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.</li> </ul> <ul style="list-style-type: none"> <li>• <b>Results in persistent or significant disability/incapacity.</b></li> </ul> <p>NOTE: Disability means a substantial disruption of a person's ability to conduct normal life's functions.</p> <ul style="list-style-type: none"> <li>• <b>Consists of a congenital anomaly or birth defect</b> (Not relevant</li> </ul>

Term	Definition
	<p>to this clinical study in infants)</p> <p><b>Other 'important medical events'</b> may also be considered serious if they jeopardize the subject or require an intervention to prevent one of the above consequences.</p> <p>For the purposes of the present clinical study, the following will also trigger SAE reporting: 1) Transfer to ICU, 2) Initiation of non-invasive respiratory support (including start of HFOT or increasing the flow above the allowed level) or invasive ventilation.</p> <p>NOTE: To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which <u>may</u> be of relatively minor medical significance (e.g., a severe rash is not likely to be an SAE, however, mild chest pain may result in a day's hospitalization and thus is an SAE).</p> <p>"Seriousness" is the regulatory definition supplied above.</p>
<b>Serious Adverse Reaction (SAR)</b>	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study medications, based on the information provided.
<b>Suspected Unexpected Serious Adverse Reaction (SUSAR)</b>	A serious adverse reaction, the nature and severity of which is not consistent with the reference safety information about the medicinal product in question set out in the IB.

#### 4.1.2. RECORDING OF ADVERSE EVENTS

<b>What will be collected</b>	All AEs
<b>Responsibility</b>	Investigator's responsibility
<b>Period of collection AEs</b>	All AEs will be reported from the time a signed and dated ICF is obtained until completion of the subject's last visit.
<b>How are AEs elicited</b>	<p>Spontaneous, unsolicited reports:</p> <ul style="list-style-type: none"> <li>- by subject, parents/caregivers and/or healthcare staff,</li> <li>- by observation (by the Investigator and/or healthcare staff),</li> <li>- by routine open questioning of the subjects (or parents/caregivers) or by the Investigator (e.g., "Is there anything new that you wish to discuss?")</li> <li>- by reviewing the diary with the subject's parent(s)/caregiver(s).</li> </ul>

<b>Where are AEs recorded</b>	Documented in the source documents and the eCRF
<b>When are AEs recorded</b>	Detailed guidance on when to complete AEs is given in the CRF completion guidelines document.

### 4.1.3. AE ASSESSMENTS

The variables to be collected for each AE are shown in the table below.

<b>What needs to be assessed for each AE?</b>	<p>For each AE, the Investigator will record his assessment of:</p> <ul style="list-style-type: none"><li>• Seriousness</li><li>• Causal relationship to study drug</li><li>• Causal relationship to study procedure</li><li>• Intensity/severity</li><li>• Action taken with study drug</li><li>• Outcome</li><li>• Medication used to treat the event</li></ul> <p>Detailed guidance on how to complete AE data is given in the CRF completion guidelines document.</p>
<b>Seriousness</b>	<p>Based on the definition of SAE above, the Investigator will assess each AE into:</p> <p>0- Non-serious (does not meet the definition of serious)</p> <p>1- Serious (meets the definition of serious)</p> <p>If the AE meets the definition of "serious", the instruction in section 4.1.4 and section 4.1.5 must be followed.</p>
<b>Causal relationship scale</b>	<p>The assessment of the causal relationship between an AE and the administration of study drug is a clinical decision based on all available information at the time of the completion of the eCRF.</p> <p>The assessment is based on whether there was a "reasonable causal relationship" to the study drug in question. The scale used for relationship to study is:</p> <ul style="list-style-type: none"><li>• Not related</li><li>• Unlikely related</li><li>• Possibly related</li><li>• Related</li><li>• Not Applicable</li></ul> <p>Detailed guidance on how to complete AE data is given in the CRF completion guidelines document.</p>



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<b>Causal relationship to study procedure</b>	<p>Assessment of causal relationship of any AE to protocol-required procedures (e.g., to anemia caused by blood sampling) can be completed with:</p> <ul style="list-style-type: none"> <li>• Yes (specify)</li> <li>• No</li> </ul>
<b>Intensity/severity scale</b>	<p>The Investigator will assess the intensity/severity of AEs on a 3-point scale:</p> <ul style="list-style-type: none"> <li>• Mild (discomfort noticed but no disruption of normal daily activity)</li> <li>• Moderate (discomfort sufficient to reduce or affect normal daily activity or requires specific treatment)</li> <li>• Severe (incapacitating, with inability to perform normal activities)</li> </ul> <p>It is emphasized that the term severe is a measure of intensity: a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.</p>
<b>Action taken with study drug</b>	<p>Action taken with study drug is to be documented as follows:</p> <ul style="list-style-type: none"> <li>• Dose not changed</li> <li>• Drug interrupted</li> <li>• Drug withdrawn</li> <li>• Not applicable</li> </ul>
<b>Outcome</b>	<p>The outcome of the AE is to be documented as follows:</p> <ul style="list-style-type: none"> <li>• Recovered/resolved</li> <li>• Recovering/resolving</li> <li>• Recovered/resolved with sequelae</li> <li>• Not recovered/not resolved</li> <li>• Fatal</li> <li>• Unknown</li> </ul>
<b>Medication used to treat the event</b>	<p>Any medications necessary for the treatment of the AE must be recorded on the concomitant medication section of the CRF. The indication should be same term used for the AE.</p>
<b>Follow-up of AEs</b>	<p>Investigators are responsible for following-up and providing complete information on the AEs up to final outcome and for responding to the Sponsor's queries in a timely manner.</p>

## 4.1.4. RECORDING OF SAEs

Collection and recording of SAEs by the Investigator	
<b>What will be collected</b>	All SAEs
<b>Period of collection</b>	<ul style="list-style-type: none"> <li>• <b>From signed informed consent to subject's last visit: All SAEs.</b></li> <li>• <b>At any time after the subject's last visit: Only SARs.</b></li> </ul> <p>SAEs assessed by the Investigator as causally related to study drug will be notified to the Sponsor even after the subject's completion of his/her participation in the Clinical Trial (e.g., delayed onset/long latency SAEs).</p>
<b>Exemptions from SAE process below</b>	None
<b>Where are SAEs recorded</b>	In addition to the recording of the AE as described in the section above, Serious AE specific information will also be recorded on the SAE form.
<b>When are SAEs recorded</b>	Within <b>24 hrs</b> of Investigator/site's first knowledge (see also section <a href="#">4.1.5</a> )
<b>How are SAEs recorded</b>	<p>Indicate whether the report is initial or follow-up.</p> <p>Attach supporting documents relevant to the SAE (e.g., hospital reports). The subject's name should be edited-out from any supporting documents.</p> <p>Whenever possible, the overall diagnosis or overall syndrome's name should be used as the SAE verbatim. If the diagnosis is not available, use signs and symptoms and provide the final diagnoses as follow-up information when available. The AE verbatim term and the SAE verbatim term should match and must be clinically equivalent.</p> <p>Include medical history and concurrent diseases that are relevant to the SAE.</p> <p>The SAE must include the Investigator's assessment of the relationship of the event to study drug.</p> <p>SAE forms must be signed by the Investigator or delegated person.</p>
<b>Causal relationship scale</b>	<p>The assessment of the causal relationship between an SAE and the administration of study drug is a clinical decision based on all available information at the time of the completion of the SAE form.</p> <p>The assessment is based on the question of whether there was a "reasonable causal relationship" to the study drug.</p> <p>The following considerations should be taken into account for this assessment:</p> <ul style="list-style-type: none"> <li>• Is the Time-to-Onset of the event compatible with a causal relationship? Was it "treatment-emergent"?</li> <li>• Is it of common occurrence in the population under study?</li> </ul>

Collection and recording of SAEs by the Investigator	
	<ul style="list-style-type: none"> <li>• Did it respond to de-challenge?</li> <li>• Did it recur on re-challenge?</li> <li>• Were there concomitant medications known to cause the event?</li> <li>• Were confirmatory laboratory/other tests done?</li> <li>• Was there a medical history of the same type of events?</li> <li>• Was there a more likely alternative cause or risk factor?</li> </ul> <p>The criteria: "a causal relationship cannot be ruled out" should not be used, as this is hardly ever possible for individual events. The question should be whether the study drug is the most likely cause of the event or whether there were other more likely causes or risk factors (underlying diseases, concomitant medication, etc.).</p> <p>-NOT RELATED (there is not a reasonable causal relationship)</p> <p>-RELATED (there is a reasonable causal relationship)</p>
<b>Follow-up SAE information</b>	<p>Investigators are responsible for following-up and providing complete information (i.e., lab reports, hospital reports) on the SAEs up to their final outcome and responding to the Sponsor's queries in a timely manner.</p> <p>For reported deaths, the Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., autopsy reports and final medical reports).</p>

#### 4.1.5. NOTIFICATION OF SAES TO SPONSOR

Investigator Notification of SAEs to the Sponsor	
<b>When</b>	Immediately and always within <b>24 hrs</b> of Investigator's/ site's first knowledge
<b>How</b>	<p><b>Conventional SAE form</b> will be completed and send by e-mail (preferred method) or FAX to:</p> <p><b>e-mail:</b> <a href="mailto:pv@ablynx.com">pv@ablynx.com</a></p> <p><b>FAX:</b> +32 9 262 00 35</p>
<b>Follow-up SAE information</b>	Collection and notification to the Sponsor will occur <b><u>in the same manner and timelines</u></b> as for initial SAEs.

## 4.1.6. SUSAR NOTIFICATION PROCESS

AE reporting, including SUSARs, will be carried out in accordance with applicable local regulations.

Expedited reporting	The Sponsor or delegated vendor(s) will expedite SUSAR or SAR reports to the regulatory authorities (PMDA), IRB and Investigators where applicable according to the following reporting timelines:			
	To PMDA:			
		Seriousness	Domestic cases	Foreign cases
	SUSAR	D/LT	Within 7 days	Within 7 days
		Others	Within 15 days	Within 15 days
SAR (Expected)	D/LT	Within 15 days	Within 15 days	
SUSAR: Suspected Unexpected Serious Adverse Reaction SAR: Serious Adverse Reaction D: Death LT: Life threatening				
To IRB and Investigators:				
Expedited reporting of SUSARs will be done immediately after the submission to PMDA.				
Distribution of SUSARs to Investigators	The Sponsor or delegated vendor will distribute the SUSARs to Investigators. This can be done in the form of individual reports or periodic line listings.			
Submission to local IRBs	Where required by IRB procedure, it is the Principal Investigator’s responsibility to notify the IRB of SUSAR reports received from the Sponsor.			

## **4.2. OTHER REPORTABLE INFORMATION**

### **4.2.1. MEDICATION ERRORS**

Medication error is defined as an error made in prescribing, dispensing, administration, and/or use of an investigational product.

Medication errors include, but are not limited to, the following:

- Administration of the wrong dosage to the subject (i.e., different from the dose prescribed by the protocol).
- Administration of study drug that has not been assigned to the subject.
- Administration of expired study drug.
- Administration by a route other than inhalation.
- Deviations to the study drug storage conditions when administered to the subject.
- Nasal cannula not removed.
- Air or oxygen tube not connected to the FOX-Flamingo inhalation system, damaged or kinked.
- Air or oxygen flow to the FOX-Flamingo inhalation system too low or too high.
- Re-use of inhalation set (i.e., the face mask, mask adapter, and nebulizer mesh/head and fill reservoir).

All medication errors that occur during the study should be reported to the Sponsor regardless of whether they are a cause of AEs/SAEs.

AE/SAEs resulting from medication errors need to be reported as any other AEs/SAEs (see section 4.1.2 and section 4.1.4) indicating the medication error.

For information on management of overdoses, please refer to section 3.3.4.3.

### **4.2.2. MEDICAL DEVICE ISSUES**

All medical device issues that occur during the study should be reported to the Sponsor regardless of whether they are a cause of AEs/SAEs.

AE/SAEs resulting from medical device issues need to be reported as any other AEs/SAEs (see section 4.1.2 and section 4.1.4) indicating the medical device issue.

## 5. STATISTICS

### 5.1. STUDY POPULATIONS

The following populations will be considered for analysis:

- **Modified Intent-to-treat (mITT) Population:** All randomized subjects who received at least 1 administration of study drug, as randomized (i.e., using the treatment to which the subject was randomized).
- **Safety Population:** All subjects who received at least 1 administration of study drug, as treated (i.e., using the treatment that the subject actually received).
- **PK population:** Subset of the subjects in the safety population for whom the primary PK data are considered to be sufficient and interpretable. For this study, this will correspond to all subjects in the safety population who received at least 1 administration of ALX-0171 and for whom at least three ALX-0171 serum concentrations have been determined.

The mITT Population will be the primary study population used for the analysis of efficacy data, the Safety Population for the analysis of safety, PD, and immunogenicity data, and the PK population for analysis of PK data.

### 5.2. STATISTICAL AND ANALYTICAL PLAN

Analysis of all parameters will be described in a Statistical Analysis Plan (SAP) and a Data Analysis Plan (DAP; for PK analysis) and will comprise all methods applied for analysis of the corresponding data. There will be no interim analysis performed in this study.

The SAP and relevant analytical plans for PK, PD and immunogenicity will be generated under responsibility of the Sponsor, and will be finalised prior to database lock. Any deviations from the reporting and analysis plans will be reported in the Section of "Changes in the planned analysis" in the Clinical Study Report (CSR).

### 5.3. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics will be summarized using descriptive statistics (including number of observations, mean, standard deviation, median, maximum, and minimum) for continuous variables and counts and percentages for categorical variables.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization (WHO) Drug Dictionary, anatomical therapeutic chemical (ATC) class and preferred term.

## ***5.4. EVALUATION OF SAFETY***

Safety and tolerability of ALX-0171 in Japanese infants and young children hospitalized for RSV LRTI will be evaluated based on the following:

- AEs will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) using the latest MedDRA version available at the time of database lock.
- A treatment-emergent analysis of AEs will be done.
- Frequency of subjects presenting with AEs, AEs leading to withdrawal, adverse drug reactions, and SAEs will be tabulated for each treatment group by system organ class and preferred term.
- For laboratory parameters, descriptive statistics (mean, median, standard error, minimum, and maximum) will be computed on the actual values and the change from baseline for each parameter. All laboratory values will be categorized according to their normal ranges as below, within or above normal.
- Other safety variables, including e.g., heart rate, need for oxygen therapy (and when applicable, relevant parameters such as duration of oxygen therapy needed, oxygen delivery mode, flow of inspired oxygen), or any significant worsening requiring immediate or intensive medical intervention, will be fully depicted using descriptive statistics.

Findings in physical examinations will be listed. Body weight and body temperature results will be summarized by descriptive statistics.

## ***5.5. EVALUATION OF PK***

Systemic (serum) concentrations of ALX-0171 will be used as a surrogate for local (lung) concentrations.

Individual study drug concentrations will be listed, e.g., in summary tables. In addition, a listing of the actual sampling times relative to the study drug administration times will be presented. If considered meaningful, geometric means and standard deviations will be added to the summary tables.

A population PK model (non-linear mixed effect modeling) will be developed based on the ALX-0171 serum concentrations from this study. The dataset will be supplemented with serum concentration data from Study ALX0171-C201, and any other studies that are

considered relevant to support model structure. The covariate analysis will include the investigation of ethnicity.

Individual PK parameters will be derived by means of empirical Bayesian estimation. The following individual PK parameters will be provided: apparent clearance (CL/F), area under the curve (AUC) as nominal (filling) dose divided by CL/F and cumulative AUC over 72 hours as an expression of the cumulated exposure during the course of treatment.

Individual PK parameters will be summarized with sample size, mean, standard deviation and coefficient of variation.

The modeling exercise will be described in a separate analysis plan and will be reported in a separate report. The main findings will be summarized in the CSR.

## ***5.6. EVALUATION OF ANTIVIRAL EFFECT***

The antiviral effect (viral load in samples from nasal swabs) parameters will be analyzed using descriptive statistics. The data will be listed and summarized in tabular and/or graphical form.

The viral load (as assessed by plaque assay and qPCR) will be characterized through parameters including time-to-below the limit of quantification (BQL), time-to-undetectability, time-weighted average change from baseline up to Day 3 and Day 14, number and percent of subjects with undetectable RSV (from Day 1 to Day 14), number and percent of subjects with BQL and change from baseline in viral load.

## ***5.7. EVALUATION OF CLINICAL ACTIVITY***

Based on the Clinical Activity Outcome Measures, the following composite scores will be calculated and summarized descriptively:

- RDAI score (based on wheezing and respiratory muscle retractions, see [Appendix 1](#)),
- RACS; based on RDAI and change in respiratory rate),
- Global Severity Score (based on respiratory parameters, medical interventions, feeding, general appearance and body temperature).

The feeding and oxygen saturation outcome measures will be used to calculate Time-to-Clinical Response. Kaplan-Meier estimates will be provided.

Subjects will be considered to have met the Clinical Response criteria when both of the following criteria are fulfilled:

- Stable oxygen saturation on room air, defined as  $SpO_2 \geq 95\%$  over a period of at least 4 hours to allow for hospital discharge.
- Adequate oral feeding which is sufficient to maintain hydration and to allow for hospital discharge, in the judgment of the Investigator.



## ***5.8. EVALUATION OF IMMUNOGENICITY***

Immunogenicity will be evaluated systemically in serum. Individual immunogenicity results will be listed, and summarized using descriptive statistics.

Prevalence of pre-Ab and incidence of TE ADA or NAb, as well as titer levels (TE ADA) and normalized ratios (NAb) of the antibody responses, will be reported.

Potential correlation between pre-Ab, TE ADA or NAb and safety, PK or efficacy will be assessed.

In case of severe and/or serious hypersensitivity reactions judged to be related to study drug occurs, a blood sample will be collected to further characterize the hypersensitivity reactions (if deemed necessary). Correlation between hypersensitivity reactions and immunogenicity results will be assessed. Results will be summarized through listing of the individual results.

## ***5.9. EVALUATION OF PD***

The PD characteristics (serum levels of KL-6) will be analyzed using descriptive statistics. The data will be listed and summarized in tabular and/or graphical form.

## **6. DATA QUALITY ASSURANCE AND DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

Audits may be conducted to evaluate systems, processes, and expertise for the subcontracted activities and to assess compliance with the contractual agreements, the protocol, applicable Standard Operating Procedures, and regulatory requirements. During or after the conduct of the study, process-related audits may be performed as well. When performed, an audit certificate will be provided in appendix of the final study report.

The clinical research facility will be monitored by the study monitor, to ensure correct performance of the study procedures and to ensure that the study is conducted according to the relevant regulatory requirements.

Regulatory authorities, the IRB, and/or the Sponsor representative may request access to all source documents, eCRFs and other study documentation for study-related monitoring, audit, IRB review, and regulatory inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study.

## **7. DATA PROTECTION**

During this clinical study, all clinical data will be identified only through an ID number in order to protect the rights of the subjects to privacy and to the protection of their personal data in compliance with all applicable laws and regulations.

## 8. ETHICS

### 8.1. ETHICAL APPROVAL

The Clinical Study Protocol(s), ICF(s) and any other written information and/or materials to be provided to the subjects' parent(s)/legal guardian(s) or the legally acceptable representative(s) will be submitted for review and approval by the IRB prior to the eligibility screening/baseline. The composition of the IRB is in accordance with the local regulations where the clinical study is conducted.

The Investigator/Sponsor (or CRO on behalf of the sponsor) will keep the IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the responsible persons. The study may be suspended pending further review by the IRB, unless suspension would jeopardize the subject's health. The Investigator will take care that all subject's parent(s)/legal guardian(s) or the legally acceptable representative(s) are kept informed.

No substantial amendments will be implemented to the study without prior IRB approval, except when required to eliminate apparent immediate hazards to subjects.

Notification of the end of the study will be sent to the IRB, within the number of days as specified by local regulations after completion of follow-up for the last subject. In case the study is ended prematurely, the IRB will be notified within the number of days as specified by local regulations, including the reasons for the premature termination. Results will be provided to the IRB according to local requirements for format and timing.

### 8.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with Japan- and ICH-GCP (including archiving of essential study documents), the Declaration of Helsinki, and the Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications).

ICH-adopted guidelines and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate local laws.

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

## **8.3. SUBJECT INFORMATION AND CONSENT**

As the potential subjects are infants or young children, subjects' parent(s), legal guardian(s) or the legally acceptable representative(s) must provide their written informed consent before enrolment of their child in the clinical study, and before any protocol-specified procedures are performed.

Freely given and written informed consent must be obtained according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used will be approved by both the Sponsor and designee and by the reviewing IRB. The informed consent will be in accordance with principles that originated in the Declaration of Helsinki, current ICH-GCP guidelines, applicable regulatory requirements, and the Sponsor's Standard Operating Procedure.

Before undertaking any study-related procedure in the study, the Investigator or an authorized member of the investigational staff must explain to the subjects' parent(s), legal guardian(s) or the legally acceptable representative(s) the aims, methods, objectives, potential clinical benefits, and potential hazards of the study, and any discomfort participation in the study may entail.

The subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) will be informed that the participation is voluntary and that they may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled, and that all data collected up to the point of withdrawal will be used and reported in an anonymized way. They will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up, if needed, and that the records may be accessed by health authorities, authorized Sponsor staff, and Sponsor representative without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. In addition, insurance coverage provided during the study will be explained.

By signing the ICF the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) is/are authorizing such access, and agrees to allow the study physician to recontact the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) for the purpose of obtaining consent for additional safety evaluations, if needed.

If the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) is/are unable to read, an impartial witness must be present during the entire informed consent discussion. Once the written ICF (and any other written information) is read and explained to the subjects' parent(s), legal guardian(s) or the legally acceptable

representative(s), and after the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) has orally consented to the subject's participation in the study, and, if capable of doing so, has signed and personally dated the ICF, the witness must sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subjects' parent(s), legal guardian(s) or the legally acceptable representative(s), and that informed consent was freely given by the subjects' parent(s), legal guardian(s) or the legally acceptable representative(s).

The language used in the oral and written information about the study, including the ICF, will be as nontechnical as practical and should be understandable to the subjects' parent(s), legal guardian(s) or the legally acceptable representative(s). They will be given sufficient time to read the ICF and given the opportunity to ask questions. After this explanation and before entry into the study, consent will be appropriately recorded by means of the subjects' parent(s), legal guardian(s) or the legally acceptable representative(s) personally dated signature(s) and by the Investigator or an authorized member of the investigational staff who conducted the ICF discussion.

After having obtained the consent, a copy of the signed ICF will be given to the subject's parent(s)/legal guardian(s) or the legally acceptable representative(s). The original of the ICF will be retained by the Investigator in the "Investigator Site File".

If any new information on the study medication which may influence the decision of the subject to continue the study becomes available, the Investigator(s) should inform the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) of such information immediately, record this in a written form, and confirm with the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) if they concur with the subject's continued participation in the study. In addition, the currently approved ICF should be revised immediately.

The Investigator(s) should re-explain the information to the subjects' parent(s), legal guardian(s), or the legally acceptable representative(s) using the updated ICF even though the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

## **8.4. PRIVACY**

The study is conducted according to the principles of ICH, including the specifications for privacy and data protection.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the

investigational study drug(s) used in this study. The collected data are adequate, and not excessive in relation to the purposes for which they are collected and processed.

The data are collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration is in place. The data will be kept in a form, which does not readily permit identification of the subject. Subjects will be identified by his/her assigned unique subject number and his/her year of birth. Personal data will only be collected and processed using these unique identification items. Only the Investigator and his/her study team keeps a list that makes it possible to link unique subject numbers to an individual name. Sponsor personnel whose responsibilities require access to personal data have to agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject's parent(s)/legal guardian(s) or the legally acceptable representative(s) includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his/her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

## **9. DATA HANDLING AND RECORD KEEPING**

### ***9.1. DISTRIBUTION OF ACTIVITIES***

Contact details of the Sponsor and third parties are available in the "Investigator Site File".

### ***9.2. DOCUMENTATION***

Study documentation required for study start (as specified in the ICH E6 Guideline for GCP [CPMP/ICH/135/95]) shall be exchanged between Ablynx NV and the vendor prior to the administration of study drug.

#### **9.2.1. CASE REPORT FORM COMPLETION**

Case report forms will be completed for each subject (incl. screen failures in order to assess the numbers and demographic characteristics of the excluded subjects, and the reasons for their exclusion).

The Investigator (or sub-Investigator) will ensure that data are recorded on the eCRF as specified in the Clinical Study Protocol and in accordance with the instructions in the eCRF completion guidelines. The Investigator (or sub-Investigator) will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRF, and of the provision of answers to data queries according to the Clinical Study Agreement. All eCRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel. The Investigator (or sub-Investigator) will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

#### **9.2.2. SOURCE DOCUMENTATION**

At a minimum, source documentation must be available for the following: informed consent process, medical history, subject identification, eligibility, and study identification; date of informed consent; dates of visits; results of all efficacy evaluations; results of safety parameters as required by the protocol; record of all AEs along with intensity and causality assessments; and follow-up of AEs; prior and concomitant medication; study drug receipt records; study drug administration information; any medical notes (original documents, data and records, e.g., laboratory data); date of study completion, and reason for early discontinuation of study procedures or withdrawal from the study (and information on documented attempts to obtain information on the final status of the subject for those who are considered lost to follow-up), if applicable.

In addition, the author of an entry in the source documents should be identifiable.



At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care (Patient's Medical File).

Following the ICH-GCP guidelines, direct access to source documentation (medical records) must be allowed.

### **9.2.3. RECORD RETENTION**

The Investigator/Institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents before, during and after the study as specified in ICH/GCP section 8, Essential Documents for the Conduct of a Clinical Study, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until the day on which the investigational product provider receives marketing approval of the test drug (or the day 3 years after the date of notification in the case of a notification pursuant to Article 26-10, Paragraph 3), or the day 3 years after the date of premature termination or completion of the clinical study, whichever comes later. These documents will be retained for a longer period if required by the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to the period and method of when these documents no longer need to be retained.

If the responsible Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/Institution must permit access to such essential documents and subject data.

### **9.2.4. MONITORING**

The monitor will perform on-site monitoring visits as specified in a monitoring plan to ensure that all aspects of the protocol, contractual agreements and regulatory requirements are followed and that subjects' human rights, safety and well-being are protected. The monitor will record dates of monitoring in a study center visit log that will be kept at the site. At these visits, the monitor will perform source data verification and check the data entered into the eCRF for completeness and accuracy. The nature and location of all source

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documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation ([electronic] medical records) must be permitted at all times. Findings from this review of captured data will be discussed with the investigational staff. The Sponsor expects that, during on-site monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits will be resolved in a timely manner.

## **10. FINANCING AND INSURANCE**

### *Insurance*

Ablynx NV holds and will maintain an adequate insurance policy covering damages arising from Ablynx-sponsored clinical research studies.

Ablynx NV will indemnify the Investigator in accordance with the provisions as set in a separate written agreement between Ablynx NV (or a vendor on behalf of the Sponsor) and the relevant Investigator/clinical site.

### *Financing*

The financial aspects of the study will be documented in an agreement between the Sponsor (or a vendor on behalf of the Sponsor) and the Head of Institution.

Reimbursement for reasonable expenses related to the study will be foreseen.

## **11. USE OF INFORMATION, REPORTING, AND PUBLICATION**

By signing this protocol, the Investigator reaffirms to the Sponsor that he or she will maintain in confidence all information furnished, or resulting from this study. He/she will only divulge such information as may be necessary to the IRB and the members of the staff and the parent(s)/legal guardian(s) of subjects who are involved in this study.

All data and records provided by the Sponsor or generated during the study (other than subject's medical records) and all data and inventions covered in the course of conducting the study, whether patentable or not, are the sole and exclusive property of the Sponsor.

The Investigator and all other study team members at any service provider involved will keep strictly confidential all information provided by the Sponsor related to this study and all data and records generated in the course of the study. They will not use the information, data, or records for any other purpose than conducting the study without prior written approval of the Sponsor.

A Coordinating Investigator will be selected among the study's Investigators based on the number of subjects overseen at the study's sites, as well as his/her scientific contributions during the conduct of the study. The Coordinating Investigator will review and contribute to the contents of the CSR prior to its approval.

Publication of any results from this study will be according to the principles of the Declaration of Helsinki, and will require prior review and written agreement of the Sponsor.

## 12. REFERENCES

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.
5. Black, C.P., *Systematic review of the biology and medical management of respiratory syncytial virus infection*. Respiratory care, 2003. **48**(3): p. 209-31; discussion 231-3.
6. Ablynx Summary Report, *Immunogenicity risk assessment ALX-0171*.
7. Chamberlain, P., *Addressing immunogenicity-related risks in an integrated manner*. Informa UK - Dossier Strategy, 2011.
8. Shankar, G., C. Pendley, and K.E. Stein, *A risk-based bioanalytical strategy for the assessment of antibody immune responses against biological drugs*. Nature biotechnology, 2007. **25**(5): p. 555-61.
9. FDA, *Guidance for Industry: Immunogenicity assessment for therapeutic protein products*. 2014.
10. Ablynx Report 24\_A001701\_14\_0038, *Immunogenicity risk assessment ALX-0171*.
11. Hall, C.B., et al., *The burden of respiratory syncytial virus infection in young children*. The New England journal of medicine, 2009. **360**(6): p. 588-98.
12. Wang, Y., et al., *Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies*. Journal of clinical pharmacology, 2012. **52**(10): p. 1601-6.
13. Boe, J., et al., *European Respiratory Society Guidelines on the use of nebulizers*. The European respiratory journal, 2001. **18**(1): p. 228-42.
14. Ablynx report 24\_A001701\_14\_0057, *Physiologically-based pharmacokinetic (PBPK) model to explore ALX-0171 pharmacokinetics in infants following inhalation*. 2014.
15. Justicia-Grande, A.J., et al., *Development and Validation of a New Clinical Scale for Infants with Acute Respiratory Infection: The ReSVinet Scale*. PloS one, 2016. **11**(6): p. e0157665.
16. Murray, *Measurement of intracellular replicative strand in Respiratory Syncytial Virus (RSV) infected human volunteers*. Poster presentation at Molecular Med Tri-Con San Francisco, CA. 2016.
17. Howie, S.R., *Blood sample volumes in child health research: review of safe limits*. Bulletin of the World Health Organization, 2011. **89**(1): p. 46-53.
18. WHO, *Paediatric clinical trials - guidance for assessors*. 2011.
19. EMA, *Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use - Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*. 2008.
20. FDA, *21CFR50 - Subpart D: Additional Safeguards for Children in Clinical Investigations*. 2013.
21. FDA, *45CFR46 - Protection of human subjects*. 2013.
22. Justicia-Grande, A., et al., *Development and validation of a new clinical scale for infants suffering from acute respiratory infection*. Leipzig: 33rd Annual Meeting of the European Society for Paediatric Infectious Diseases, 2015.
23. Cebey-Lopez, M., et al., *Bacteremia in Children Hospitalized with Respiratory Syncytial Virus Infection*. PloS one, 2016. **11**(2): p. e0146599.

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24. Barrett, J.S., et al., *Physiologically based pharmacokinetic (PBPK) modeling in children*. Clinical pharmacology and therapeutics, 2012. **92**(1): p. 40-9.
25. De Paepe, M.E., et al., *Postmortem lung weight/body weight standards for term and preterm infants*. Pediatric pulmonology, 2005. **40**(5): p. 445-8.

## 13. APPENDICES

### 13.1. APPENDIX 1: RDAI AND RACS

The Respiratory Distress Assessment Instrument (RDAI) score is a 17-point score based on wheezing and retraction.

Variable	Number of Points					
	0	1	2	3	4	Max Points
Wheezing						
Expiration	None	End	1-2	3-4	All	4
Inspiration	None	Part	All	NA	NA	2
Location	None	Segmental, ≤2-4 lung fields	Diffuse, ≥3-4 lung fields	NA	NA	2
Retractions						
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.

The Respiratory Assessment Change Score (RACS) is the sum of the change in the RDAI score and a standardized score for the change in respiratory rate. The change in respiratory rate is assigned 1 point per each 10% change in the respiratory rate.

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

## 13.2. APPENDIX 2: GLOBAL SEVERITY SCORE

The Global Severity Score is the sum of the scores of the 7 individual items as described below; total maximum score is 20 points; higher score indicates more severe disease.

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, 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	No wheezing and no retractions
	1-2-3	Points will be attributed uniformly across the 17 points for RDAI
Respiratory rate	0-1-2-3	Points will be attributed uniformly across the respiratory rate values for each age range
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)



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