Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter dose ranging study of ALX-0171 in infants and young children hospitalized for respiratory syncytial virus lower respiratory tract infection

Summary

EudraCT number	2016-001651-49
Trial protocol	GB DE LV HU ES EE LT SK BE BG CZ Outside EU/EEA PL HR
Global end of trial date	25 May 2018

Results information

Result version number	v2 (current)
This version publication date	13 June 2019
First version publication date	25 April 2019
Version creation reason	• New data added to full data set The record will be updated to bring the EU clinical trials record in line with the clinicaltrials.gov results record (e.g., additional data on immunogenicity will be added).

Trial information

Trial identification

Sponsor protocol code	ALX0171-C201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02979431
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ablynx NV
Sponsor organisation address	Technologie Park 21, Zwijnaarde, Belgium, 9052
Public contact	clinicaltrials@ablynx.com, Ablynx NV, +32 (0)9262 00 00, clinicaltrials@ablynx.com
Scientific contact	clinicaltrials@ablynx.com, Ablynx NV, +32 (0)9262 00 00, clinicaltrials@ablynx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001553-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2018
Global end of trial reached?	Yes
Global end of trial date	25 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the anti-viral effect and safety of different doses of inhaled ALX-0171 in subjects hospitalized for respiratory syncytial virus (RSV) lower respiratory tract infection.

Protection of trial subjects:

Written informed consent was obtained according to local requirements after the nature of the study was fully explained to the parent/ legal representative and before performance of any study-related activity. The informed consent form (ICF) was approved by both the Sponsor and the reviewing IEC/IRB. The ICF was in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy. Before undertaking any study-related procedure, the Investigator or an authorized member of the investigational staff explained to the parents/legal representatives of potential subjects the aims, methods, objectives, potential lack of clinical benefit, and potential hazards of the study, and any discomfort participation in the study would entail. The parents/ legal representatives were informed that their participation was voluntary and that they could refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the subject was otherwise entitled to and that all data collected up to the point of withdrawal would be used and reported in an anonymous way. Only subjects who met all the study inclusion criteria and none of the exclusion criteria were to be randomized to study treatment. Close monitoring of all subjects was to be adhered to throughout the study.

Background therapy:

The treatment and care provided to each subject were 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 (2014), could also be followed. Permitted treatment/ medications included (but were not limited to) the following:
-O2 supplementation through nasal cannula, via face mask or headbox. The initiation, monitoring and weaning of oxygen supplementation followed local practice. It should be removed for the nebulized study drug administration, during which air or oxygen flow of 2 L/min was provided
-Fluid/food supplementation (i.v. or via nasogastric tube, if applicable)
-Antipyretics and/or nonsteroidal anti-inflammatory medication
-Hypertonic saline (but not within 4 hours before start or 4 hours after the end of study drug administration)
-Short acting β2-agonists
-Antibiotics (in case of secondary bacterial infection)
-Epinephrine
-Anticholinergics

Evidence for comparator:

Not applicable. This was a placebo-controlled study; the placebo group served as comparator group for the 3 ALX-0171 treatment groups (ALX-0171 target concentrations: 3.0mg/kg, 6.0mg/kg, and 9.0mg/kg).

Actual start date of recruitment	11 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Croatia: 23
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Latvia: 10
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Philippines: 5
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Colombia: 1
Worldwide total number of subjects	180
EEA total number of subjects	142

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	180
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Subject First Visit: 11 January 2017, Last Subject Last Visit: 25 May 2018
Subjects were enrolled in 50 sites in 16 countries: Belgium, Bulgaria,Chile, Colombia, Croatia, Czech Republic, Germany, Hungary, Israel, Latvia, Malaysia, Philippines, Poland, Slovakia, Spain, and Thailand.

Pre-assignment

Screening details:

A total of 301 subjects were screened. 180 subjects were randomized to study drug treatment. Five subjects were randomized but not treated with study drug. Of those, 2 subjects discontinued as the parent/guardian withdrew consent, 2 subjects were randomized in error without receiving study drug, and 1 subject discontinued due to an AE of dyspnoea.

Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

To ensure blinding across dose groups, study drug was administered via inhalation using 2 consecutive nebulizations; 2X ALX-0171 nebulizations, or 1X ALX-0171 and 1X placebo, or x2 placebo depending on the assigned treatment group. To protect the integrity of the data, treatment assignment was kept blinded for investigative sites, parent(s)/legal guardian(s) and caregiver(s), site monitors, other study team members until the final database lock. No unblinding by the site occurred for the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation 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.

Arm type	Placebo
Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days.

Arm title	ALX-0171 3.0mg/kg

Arm description:

Subjects in this arm received a target ALX-0171 dose of 3.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.

Arm type	Experimental

Investigational medicinal product name	ALX-0171
Investigational medicinal product code	
Other name	ALX-0171 Nanobody
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ALX-0171 at target concentration of 3.0mg/kg was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. To achieve double-blinding across the different groups, each dose was administered as 2 consecutive nebulizations (i.e., 2 nebulizations of ALX-0171, or one nebulization of ALX-0171 and one of placebo, or 2 nebulizations of placebo depending on the treatment group assigned).

Arm title	ALX-0171 6.0mg/kg

Arm description:

Subjects in this arm received a target ALX-0171 dose of 6.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.

Arm type	Experimental
Investigational medicinal product name	ALX-0171
Investigational medicinal product code	
Other name	ALX-0171 Nanobody
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ALX-0171 at target concentration of 6.0mg/kg was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. To achieve double-blinding across the different groups, each dose was administered as 2 consecutive nebulizations (i.e., 2 nebulizations of ALX-0171, or one nebulization of ALX-0171 and one of placebo, or 2 nebulizations of placebo depending on the treatment group assigned).

Arm title	ALX-0171 9.0mg/kg

Arm description:

Subjects in this arm received a target ALX-0171 dose of 9.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.

Arm type	Experimental
Investigational medicinal product name	ALX-0171
Investigational medicinal product code	
Other name	ALX-0171 Nanobody
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ALX-0171 at target concentration of 9.0mg/kg was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. To achieve double-blinding across the different groups, each dose was administered as 2 consecutive nebulizations (i.e., 2 nebulizations of ALX-0171, or one nebulization of ALX-0171 and one of placebo, or 2 nebulizations of placebo depending on the treatment group assigned).

Number of subjects in period 1[1]	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg
Started	42	45	43
Included in the mITT Population	42	45	43
Completed	40	44	43
Not completed	2	1	0
Other	1	-	-
Withdrawal by parent/guardian	1	1	-

Number of subjects in period 1[1]	ALX-0171 9.0mg/kg
Started	45
Included in the mITT Population	45
Completed	44
Not completed	1
Other	-
Withdrawal by parent/guardian	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 301 subjects were screened. Of those, 121 subjects (40.2%) were considered screening failures. A total of 180 subjects were randomized in the study (placebo: 44 subjects; ALX-0171 3.0 mg/kg: 46; 6.0 mg/kg: 45; 9.0 mg/kg: 45). Five subjects were randomized but they were not treated with study drug. Demography and Baseline Disease characteristics are reported for the mITT Population. Therefore, the number of subjects/group shown are those in the mITT Population.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation 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.	
Reporting group title	ALX-0171 3.0mg/kg
Reporting group description:	
Subjects in this arm received a target ALX-0171 dose of 3.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.	
Reporting group title	ALX-0171 6.0mg/kg
Reporting group description:	
Subjects in this arm received a target ALX-0171 dose of 6.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.	
Reporting group title	ALX-0171 9.0mg/kg
Reporting group description:	
Subjects in this arm received a target ALX-0171 dose of 9.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.	

Reporting group values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg
Number of subjects	42	45	43
Age categorical			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
< 6 months	24	23	27
≥ 6 months and < 12 months	8	13	7
≥ 12 months	10	9	9
Age continuous			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45). The age reported is the age at the time of informed consent signing.			
Units: months			
arithmetic mean	6.964	6.933	6.657
standard deviation	± 6.0668	± 5.8827	± 6.2605
Gender categorical			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
Female	24	15	19
Male	18	30	24

Race			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
Asian	7	7	3
Black or African American	0	0	1
Multiple	0	0	2
Other	0	0	1
White	35	38	36
Ethnicity			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
Hispanic or Latino	4	4	5
Not Hispanic or Latino	38	41	38
Weight category			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
≥ 3.0 kg and < 4.0 kg	1	2	0
≥ 4.0 kg and < 5.0 kg	8	6	13
≥ 5.0 kg and < 7.0 kg	15	15	11
≥ 7.0 kg and < 10.0 kg	11	17	12
≥ 10.0 kg and < 12.0 kg	6	4	7
≥ 12.0 kg and < 15.0 kg	1	1	0
Gestational age			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Weeks			
arithmetic mean	38.5	38.6	38.6
standard deviation	± 1.78	± 1.99	± 1.62
Weight			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: kilogram(s)			
arithmetic mean	7.065	7.188	6.988
standard deviation	± 2.4193	± 2.2278	± 2.4084
Height			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: centimeter			
arithmetic mean	65.84	65.71	65.25
standard deviation	± 9.997	± 10.210	± 10.190
RSV titers at Baseline by plaque assay			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Log10 PFU/mL			
arithmetic mean	3.155	3.078	3.023
standard deviation	± 0.2531	± 0.2259	± 0.2438
RSV titers at Baseline by RT-qPCR			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Log10 copies/mL			
arithmetic mean	4.731	4.623	5.040

standard deviation	± 0.3266	± 0.2519	± 0.2250
Number of days between symptom onset and first dose of study drug			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: days			
arithmetic mean	3.16	3.34	3.23
standard deviation	± 1.207	± 1.144	± 0.845
Global Severity Score			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: score			
arithmetic mean	9.1	9.2	9.3
standard deviation	± 2.44	± 2.00	± 2.09
RDAI score			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: score			
arithmetic mean	8.5	8.41	8.74
standard deviation	± 3.74	± 4.07	± 3.19

Reporting group values	ALX-0171 9.0mg/kg	Total	
Number of subjects	45	175	
Age categorical			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
< 6 months	25	99	
≥ 6 months and < 12 months	12	40	
≥ 12 months	8	36	
Age continuous			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45). The age reported is the age at the time of informed consent signing.			
Units: months			
arithmetic mean	7.022		
standard deviation	± 5.6884	-	
Gender categorical			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
Female	17	75	
Male	28	100	
Race			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
Asian	10	27	
Black or African American	0	1	
Multiple	0	2	
Other	3	4	
White	32	141	
Ethnicity			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			

Units: Subjects			
Hispanic or Latino	5	18	
Not Hispanic or Latino	40	157	
Weight category			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Subjects			
≥ 3.0 kg and < 4.0 kg	2	5	
≥ 4.0 kg and < 5.0 kg	7	34	
≥ 5.0 kg and < 7.0 kg	14	55	
≥ 7.0 kg and < 10.0 kg	19	59	
≥ 10.0 kg and < 12.0 kg	1	18	
≥ 12.0 kg and < 15.0 kg	2	4	
Gestational age			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Weeks			
arithmetic mean	38.3		
standard deviation	± 1.54	-	
Weight			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: kilogram(s)			
arithmetic mean	7.020		
standard deviation	± 2.2474	-	
Height			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: centimeter			
arithmetic mean	66.55		
standard deviation	± 9.580	-	
RSV titers at Baseline by plaque assay			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Log10 PFU/mL			
arithmetic mean	2.140		
standard deviation	± 0.2286	-	
RSV titers at Baseline by RT-qPCR			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: Log10 copies/mL			
arithmetic mean	4.008		
standard deviation	± 0.3070	-	
Number of days between symptom onset and first dose of study drug			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: days			
arithmetic mean	3.25		
standard deviation	± 1.149	-	
Global Severity Score			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: score			
arithmetic mean	9.4		

standard deviation	± 2.41	-	
RDAI score			
The numbers shown are of subjects included in the mITT Population (placebo N=42; ALX-0171 3.0mg/kg N=45; 6.0mg/kg N=43; 9.0mg/kg N=45).			
Units: score			
arithmetic mean	8.11		
standard deviation	± 3.80	-	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation 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.

Reporting group title	ALX-0171 3.0mg/kg

Reporting group description:

Subjects in this arm received a target ALX-0171 dose of 3.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.

Reporting group title	ALX-0171 6.0mg/kg

Reporting group description:

Subjects in this arm received a target ALX-0171 dose of 6.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.

Reporting group title	ALX-0171 9.0mg/kg

Reporting group description:

Subjects in this arm received a target ALX-0171 dose of 9.0mg/kg. ALX-0171 was administered via inhalation using the FOX-Flamingo inhalation system (using 2 consecutive nebulizations), once daily for 3 consecutive days. The formulation of ALX-0171 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.

Subject analysis set title	Intent-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of all randomized subjects.

Subject analysis set title	modified Intent-to-Treat (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

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

Subject analysis set title	RSV-Infected Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

RSV-Infected population (confirmed in central laboratory by RT-qPCR):
Although a positive local RSV test was required for eligibility assessment, a central RSV test was used for defining the RSV-Infected population. The RSV-Infected population consisted of all randomized subjects with RSV infection, as confirmed by RT-qPCR (hVIVO quantitative PCR assay) on Day 1 (pre- or post-dose), who received at least 1 administration of study drug. Subjects were classified as randomized when using this population. Dedicated outputs on the RSV-Infected population were created only if this population differed from the mITT population.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all subjects who received at least 1 administration of study drug. When using this population, the subjects were classified as treated (i.e., using the treatment that the subject actually received). This was the primary population for the analysis of prior/concomitant

medications, exposure, safety and immunogenicity data.

Primary: Time-to-below quantification limit (BQL) (plaque assay analysis)	
End point title	Time-to-below quantification limit (BQL) (plaque assay analysis)

End point description:

The primary endpoint for this trial was the time needed for the viral load to drop below the quantification limit (time-to-BQL) of the plaque assay in nasal mid-turbinate swab specimens. Time-to-BQL was defined as the time from the first study drug administration to the first occurrence of a value below the quantification limit (BQL), provided the next measured value was also below the limit of quantification. The time to BQL for subjects with missing data and/or who did not reach BQL during the trial were censored at the last non-missing viral load assessment. The primary endpoint was analysed using log-rank test to compare time-to-BQL between each of the ALX-0171 treatment groups and the combined placebo group. The tests were performed in a sequential way to preserve the family-wise error rate at 0.05. The comparisons were performed in the following order: ALX-0171 9 mg vs Placebo, followed by ALX-0171 6mg vs Placebo, ALX-0171 3mg/kg vs Placebo.

End point type	Primary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42[1]	45[2]	43[3]	45[4]
Units: hours				
median (confidence interval 95%)	46.1 (29.33 to 94.42)	14.2 (5.17 to 26.28)	5.1 (4.78 to 24.72)	5.1 (4.97 to 5.17)

Notes:

[1] - mITT Population

[2] - mITT Population

[3] - mITT Population

[4] - mITT Population

Statistical analyses

Statistical analysis title	ALX-0171 9.0mg/kg versus placebo

Statistical analysis description:

The primary endpoint was analysed using log-rank test to compare time-to-BQL between each of the ALX-0171 treatment groups and the combined placebo group. The tests were performed in a sequential way to preserve the family-wise error rate at 0.05.

Comparison groups	Placebo v ALX-0171 9.0mg/kg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	Logrank
Parameter estimate	Median time-to-BQL

Notes:

[5] - Survival Analysis using lon-rank test

Statistical analysis title	ALX-0171 6.0mg/kg versus placebo

Statistical analysis description:

The primary endpoint was analysed using log-rank test to compare time-to-BQL between each of the ALX-0171 treatment groups and the combined placebo group. The tests were performed in a sequential way to preserve the family-wise error rate at 0.05.

Comparison groups	Placebo v ALX-0171 6.0mg/kg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.001
Method	Logrank
Parameter estimate	Median time-to-BQL

Notes:

[6] - Survival analysis using log-rank test

Statistical analysis title	ALX-0171 3.0mg/kg versus placebo

Statistical analysis description:

The primary endpoint was analysed using log-rank test to compare time-to-BQL between each of the ALX-0171 treatment groups and the combined placebo group. The tests were performed in a sequential way to preserve the family-wise error rate at 0.05.

Comparison groups	ALX-0171 3.0mg/kg v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	Logrank
Parameter estimate	Median time-to-BQL

Notes:

[7] - Survival analysis using log-rank test

Secondary: Change from Baseline in Global Severity Score on Day 2 (5 hours post-dose)

End point title	Change from Baseline in Global Severity Score on Day 2 (5 hours post-dose)

End point description:

A formal comparison for change from Baseline in GSS to Day 2, 5 hours post-dose was performed using a contrast analysis on a longitudinal mixed model with random factor subject and fixed effects baseline value, treatment group and timepoint, including the treatment-by-timepoint interaction term. All data up to and including Day 3 were used in the longitudinal mixed model. The Kenward-Roger approximation of degrees of freedom was used. The model was fitted using an unstructured variance-covariance matrix. The individual pair-wise comparisons were reported (comparison in least square [LS] means for 3.0 mg/kg versus placebo; 6.0mg/kg versus placebo; 9.0 mg/kg versus placebo).

End point type	Secondary

End point timeframe:

Day 2 (5 hours post-dose)

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42[8]	45[9]	43[10]	45[11]
Units: score				
least squares mean (standard error)	-3.6392 (± 0.4160)	-3.8548 (± 0.4103)	-4.1296 (± 0.4129)	-4.2844 (± 0.4099)

Notes:

[8] - mITT Population

[9] - mITT Population

[10] - mITT Population

[11] - mITT Population

Statistical analyses

Statistical analysis title	GSS;9.0mg/kg vs placebo comparison

Statistical analysis description:

A comparison for change from Baseline in GSS to Day 2, 5 hours post-dose was performed using a contrast analysis on a longitudinal mixed model with random factor subject and fixed effects baseline value, treatment group and timepoint, including the treatment-by-timepoint interaction term. All data up to + including Day 3 were used in the longitudinal mixed model. The Kenward-Roger approximation of degrees of freedom was used.The model was fitted using an unstructured variance-covariance matrix.

Comparison groups	Placebo v ALX-0171 9.0mg/kg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.271
Method	Mixed models analysis
Parameter estimate	Difference in LS means

Notes:

[12] - Contrast analysis using a longitudinal mixed model

Statistical analysis title	GSS;6.0mg/kg vs placebo comparison

Statistical analysis description:

A comparison for change from Baseline in GSS to Day 2, 5 hours post-dose was performed using a contrast analysis on a longitudinal mixed model with random factor subject and fixed effects baseline value, treatment group and timepoint, including the treatment-by-timepoint interaction term. All data up to + including Day 3 were used in the longitudinal mixed model. The Kenward-Roger approximation of degrees of freedom was used.The model was fitted using an unstructured variance-covariance matrix.

Comparison groups	Placebo v ALX-0171 6.0mg/kg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.404
Method	Mixed models analysis
Parameter estimate	Difference in LS means

Notes:

[13] - Contrast analysis using a longitudinal mixed model

Statistical analysis title	GSS;3.0mg/kg vs placebo comparison

Statistical analysis description:

A comparison for change from Baseline in GSS to Day 2, 5 hours post-dose was performed using a contrast analysis on a longitudinal mixed model with random factor subject and fixed effects baseline value, treatment group and timepoint, including the treatment-by-timepoint interaction term. All data

up to + including Day 3 were used in the longitudinal mixed model. The Kenward-Roger approximation of degrees of freedom was used.The model was fitted using an unstructured variance-covariance matrix.

Comparison groups	Placebo v ALX-0171 3.0mg/kg
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.713
Method	Mixed models analysis
Parameter estimate	Difference in LS means

Notes:

[14] - Contrast analysis using a longitudinal mixed model

Secondary: Time-to-clinical response

End point title	Time-to-clinical response

End point description:

The time-to-clinical response was defined as the time between the first study drug administration and the time of achieving adequate oxygen saturation and adequate oral feeding.

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42[15]	45[16]	43[17]	45[18]
Units: hours				
median (confidence interval 95%)				
Time-to-clinical response	47.9 (29.17 to 64.08)	44.1 (28.33 to 51.20)	27.9 (21.08 to 43.68)	46.3 (38.00 to 50.38)
Time-to adequate oral feeding	43.7 (22.50 to 47.58)	44.0 (25.92 to 52.00)	17.6 (6.50 to 25.85)	23.8 (17.17 to 38.00)
Time-to-adequate oxygen saturation	53.4 (28.70 to 71.78)	38.5 (24.75 to 61.93)	29.5 (20.75 to 47.43)	46.5 (42.15 to 48.25)

Notes:

[15] - mITT Population

[16] - mITT Population

[17] - mITT Population

[18] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-BQL (RT-qPCR)

End point title	Time-to-BQL (RT-qPCR)

End point description:

The upper limit of CI could not be calculated; Values of the 25% percentile are reported here.

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42[19]	45[20]	43[21]	45[22]
Units: hours				
median (confidence interval 95%)	26.7 (5.00 to 49.92)	26.8 (5.17 to 44.62)	28.9 (18.25 to 49.25)	6.3 (4.97 to 25.25)

Notes:

[19] - mITT Population

[20] - mITT Population

[21] - mITT Population

[22] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-undetectable viral load

End point title	Time-to-undetectable viral load

End point description:

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35[23]	40[24]	40[25]	38[26]
Units: hours				
median (confidence interval 95%)				
plaque assay analysis	95.9 (47.23 to 121.82)	26.3 (20.25 to 28.92)	21.0 (4.88 to 28.25)	5.1 (5.00 to 5.87)

Notes:

[23] - RSV-Infected Population

[24] - RSV-Infected Population

[25] - RSV-Infected Population

[26] - RSV-Infected Population

Attachments (see zip file)	Time to undetectable viral load (RT-qPCR) /Time to Time to undetectable viral load (plaque assay)/Time to

Statistical analyses

No statistical analyses for this end point

Secondary: Viral load changes from Baseline (plaque assay analysis)

End point title	Viral load changes from Baseline (plaque assay analysis)

End point description:

Change from Baseline in RSV Load measured by Plaque Assay (RSV Infected Population)

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35[27]	40[28]	40[29]	38[30]
Units: log10 pfu/mL				
arithmetic mean (standard error)				
Baseline	3.494 (± 0.2396)	3.312 (± 0.2165)	3.135 (± 0.2430)	2.385 (± 0.2526)
Day 1, 5 hours post-dose	-0.270 (± 0.1607)	-2.173 (± 0.2123)	-2.189 (± 0.2676)	-1.535 (± 0.2526)
Day 3, 2 hours post-dose	-1.936 (± 0.2317)	-2.396 (± 0.2234)	-2.134 (± 0.2525)	-1.516 (± 0.2558)
Follow-up	-2.368 (± 0.2946)	-2.431 (± 0.2202)	-2.279 (± 0.2576)	-1.416 (± 0.2821)

Notes:

[27] - RSV-InfectedPopulation;Evaluable subjects BSL n=34; D1(5h post-dose)n=30;D3(2h post-dose) n=29;FUn=30

[28] - RSV-InfectedPopulation;Evaluable subjects BSL n=38; D1(5h post-dose)n=33;D3(2h post-dose) n=36;FUn=37

[29] - RSV-InfectedPopulation;Evaluable subjects BSL n=39; D1(5h post-dose)n=38;D3(2h post-dose) n=33;FUn=35

[30] - RSV-InfectedPopulation;Evaluable subjects BSL n=37; D1(5h post-dose)n=37;D3(2h post-dose) n=35;FUn=32

Statistical analyses

No statistical analyses for this end point

Secondary: Viral load changes from Baseline (RT-qPCR)

End point title	Viral load changes from Baseline (RT-qPCR)

End point description:

Viral load changes from baseline measured by RT-qPCR in the RSV-infected Population. The RSV-Infected Population comprised subjects with positive RSV test by central laboratory. Although a positive local RSV test was required for eligibility assessment, a central RSV test was used for defining the RSV-Infected population. For the RT-qPCR data, the median change from Baseline could not be estimated and thus values are entered where possible.

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35[31]	40[32]	40[33]	38[34]
Units: log10 copies/mL				
arithmetic mean (standard error)				
Baseline	5.236 (± 0.2827)	4.966 (± 0.2095)	5.232 (± 0.1899)	4.525 (± 0.2937)
Day 1, 5 hours post-dose	-0.221 (± 0.1601)	-0.544 (± 0.1286)	-0.241 (± 0.2031)	-0.449 (± 0.1883)
Day 3, 2 hours post-dose	-2.156 (± 0.2454)	-2.589 (± 0.2138)	-2.310 (± 0.2797)	-2.025 (± 0.2840)
Follow-up	-3.413 (± 0.3715)	-3.665 (± 0.2203)	-3.972 (± 0.2032)	-3.033 (± 0.3252)

Notes:

[31] - RSV-InfectedPopulation;Evaluable subjects BSL n=35; D1(5h post-dose)n=34;D3(2h post-dose) n=34;FUn=33

[32] - RSV-InfectedPopulation;Evaluable subjects BSL n=40; D1(5h post-dose)n=40;D3(2h post-dose) n=38;FUn=39

[33] - RSV-InfectedPopulation;Evaluable subjects BSL n=40; D1(5h post-dose)n=40;D3(2h post-dose) n=38;FUn=38

[34] - RSV-InfectedPopulation;Evaluable subjects BSL n=38; D1(5h post-dose)n=38;D3(2h post-dose) n=36;FUn=33

Statistical analyses

No statistical analyses for this end point

Secondary: Viral Load Time-weighted Average Changes from Baseline (plaque assay analysis)

End point title	Viral Load Time-weighted Average Changes from Baseline (plaque assay analysis)

End point description:

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35[35]	40[36]	40[37]	38[38]
Units: log10 pfu/mL				
arithmetic mean (standard error)				
Baseline	3.494 (± 0.2396)	3.312 (± 0.2165)	3.135 (± 0.2430)	2.385 (± 0.2526)
Day 3	-1.014 (± 0.1540)	-1.924 (± 0.1659)	-1.804 (± 0.2098)	-1.330 (± 0.2434)
Day 14 (Follow-Up)	-2.096 (± 0.2443)	-2.295 (± 0.2116)	-2.028 (± 0.2217)	-1.419 (± 0.2488)

Notes:

[35] - RSV-Infected Population; Baseline n=34; Day3 n=33;Day14 (FU) n=33, where n=evaluable subjects/group

[36] - RSV-Infected Population; Baseline n=38; Day3 n=37;Day14 (FU) n=37, where n=evaluable

subjects/group
[37] - RSV-Infected Population; Baseline n=39; Day3 n=38;Day14 (FU) n=38, where n=evaluable subjects/group
[38] - RSV-Infected Population; Baseline n=37; Day3 n=37;Day14 (FU) n=37, where n=evaluable subjects/group

Statistical analyses

No statistical analyses for this end point

Secondary: Viral Load Time-weighted Average Changes from Baseline (RT-qPCR analysis)

End point title	Viral Load Time-weighted Average Changes from Baseline (RT-qPCR analysis)

End point description:

End point type	Secondary

End point timeframe:
Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35[39]	40[40]	40[41]	38[42]
Units: log10 copies/mL				
arithmetic mean (standard error)				
Baseline	5.236 (± 0.2827)	4.966 (± 0.2095)	5.232 (± 0.1899)	4.525 (± 0.2937)
Day 3	-0.933 (± 0.1421)	-1.209 (± 0.1301)	-1.113 (± 0.1932)	-0.842 (± 0.1842)
Day 14 (Follow-up)	-2.684 (± 0.2263)	-2.828 (± 0.2099)	-2.756 (± 0.1831)	-2.292 (± 0.2581)

Notes:
[39] - RSV-Infected Population
[40] - RSV-Infected Population
[41] - RSV-Infected Population
[42] - RSV-Infected Population

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Incidence of of Treatment-emergent Anti-drug Antibodies

End point title	Immunogenicity: Incidence of of Treatment-emergent Anti-drug Antibodies

End point description:

The incidence of treatment-emergent anti-drug antibodies (TE ADA) and ADA status based on ADA assay by treatment group - safety population. Blood samples were collected at Baseline and on Day 14.
The results are categorized as follows:
- Total TE ADA positive: Post-dose sample ADA positive or in case pre-dose sample is ADA positive, post-dose sample ADA positive and significant increase in titer post-dose versus pre-dose. The increase

of the log10titer post-dose versus pre-dose should be > log10(Minimum Significant Ratio).
- Total TE ADA negative: Post-dose sample ADA negative.
- TE ADA equivocal: Pre -and post-dose sample ADA positive and no significant increase in titer post-dose versus pre-dose.
- TE ADA inconclusive: No pre-dose or post-dose sample available.
The Safety Population consisted of all subjects who received at least 1 administration of study drug. Number of subjects with non-missing ADA results were: placebo: 39; ALX-0171 3.0mg/kg: 45; 6.0mg/kg: 44; 9.0mg/kg: 46

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[43]	45[44]	43[45]	45[46]
Units: percentage				
number (not applicable)				
Total TE ADA positive	25.6	33.3	36.4	32.6
Total TE ADA negative	41.0	37.8	31.8	28.3
TE ADA equivocal	30.8	26.7	29.5	30.4
TE ADA inconclusive	2.6	2.2	2.3	8.7

Notes:

[43] - Safety Population N=40; The denominator in the placebo group for the ADA results is N=39

[44] - Safety Population N=45

[45] - Safety Population N=44

[46] - Safety Population N=46

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Incidence of of Treatment-emergent Neutralizing Antibodies

End point title	Immunogenicity: Incidence of of Treatment-emergent Neutralizing Antibodies

End point description:

Incidence of treatment-emergent neutralizing antibodies (TE NAb) as detected with the competitive ligand binding NAb assay. Blood samples for immunogenicity assessments were collected at Baseline and on Day 14.
The Safety Population consisted of all subjects who received at least 1 administration of study drug. When using this population, the subjects were classified as treated (i.e., using the treatment that the subject actually received). Number of subjects with non-missing ADA results were: placebo: 39; ALX-0171 3.0mg/kg: 45; 6.0mg/kg: 44; 9.0mg/kg: 46.

End point type	Secondary

End point timeframe:

Overall Study Period

End point values	Placebo	ALX-0171 3.0mg/kg	ALX-0171 6.0mg/kg	ALX-0171 9.0mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[47]	45[48]	43[49]	45[50]
Units: percentage				
number (not applicable)				
Post-dose Positive	5.1	24.4	40.9	26.1
Post-dose Negative	92.3	73.3	59.1	67.4
Post-dose Missing	2.6	2.2	0	6.5

Notes:

[47] - Safety Population N=40; The denominator in the placebo group for the ADA results is N=39

[48] - Safety Population N=45

[49] - Safety Population N=44

[50] - Safety Population N=46

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were reported from the time of a signed/dated ICF until the completion of the subject's last visit.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Includes the number of subjects in the placebo group included in the Safety Population.

Reporting group title	ALX-0171 3.0 mg/kg

Reporting group description:

Subjects included in ALX-0171 3.0mg/kg teatment group in the Safety Population.

Reporting group title	ALX-0171 6.0 mg/kg

Reporting group description:

Subject included in the ALX-0171 6.0 mg/kg treatment group in the Safety Population

Reporting group title	ALX-0171 9.0 mg/kg

Reporting group description:

Subjects included in the ALX-0171 9.0mg/kg treatment group in the Safety Population.

Serious adverse events	Placebo	ALX-0171 3.0 mg/kg	ALX-0171 6.0 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 40 (12.50%)	4 / 45 (8.89%)	3 / 44 (6.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Vessel puncture site phlebitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 40 (0.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 40 (2.50%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	1 / 40 (2.50%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 40 (2.50%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	1 / 40 (2.50%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 40 (2.50%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ALX-0171 9.0 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 46 (6.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Vessel puncture site phlebitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchiolitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumococcal bacteraemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia viral			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	ALX-0171 3.0 mg/kg	ALX-0171 6.0 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 40 (42.50%)	23 / 45 (51.11%)	21 / 44 (47.73%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 45 (4.44%)	4 / 44 (9.09%)
occurrences (all)	1	3	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 40 (5.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	1 / 40 (2.50%)	6 / 45 (13.33%)	3 / 44 (6.82%)
occurrences (all)	1	7	3
Cough			
subjects affected / exposed	1 / 40 (2.50%)	2 / 45 (4.44%)	3 / 44 (6.82%)
occurrences (all)	1	2	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 40 (5.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 40 (7.50%)	3 / 45 (6.67%)	3 / 44 (6.82%)
occurrences (all)	3	3	4
Conjunctivitis			
subjects affected / exposed	2 / 40 (5.00%)	2 / 45 (4.44%)	1 / 44 (2.27%)
occurrences (all)	2	2	1
Rhinitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Otitis media			

subjects affected / exposed	3 / 40 (7.50%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	ALX-0171 9.0 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 46 (32.61%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Rhinitis			

subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2016	-Criteria for stopping dose escalation during the sequential part of the study, as well as specifications for which doses could be used in the parallel part of the study, were added. The individual discontinuation criteria were updated to ensure consistency with the dose-escalation stopping criteria. -Inclusion criterion 2 was updated to allow inclusion of subjects weighing up to < 15.0 kg. -For clarity, the exclusion criterion on HIV positivity was reworded and an additional criterion was added to exclude subjects with a known hypersensitivity to the study drug or any excipient of the study drug from the study. -Instructions for dosing were updated with additional weight bands and safety margin calculation was updated accordingly. -Detailed guidance on early detection and treatment of the potential risks of airway hyperreponsiveness and immediate or delayed adverse drug reactions were added.
30 October 2017	1. The non-interventional, Follow-up Study ALX-0171 C202 was deleted, as it will not be conducted; following interactions between the Sponsor and the European Medicines Agency's Paediatric Committee, the study was removed from the product's Paediatric Investigation Plan. 2. The age range for study population was updated for consistency (age range reads: 28 days to < 2 years). 3. The Schedule of Assessments underwent changes for clarity and easier flow in the assessments to be performed: - On Day 1, the time window before study drug administration was extended to 3 hour - Time windows of 0.5 hours before and after the 2-hour post-dose assessments were added to allow additional time for the site staff to perform the assessments. - To enhance the overview, the randomization row was moved. - Additional guidance was added on the footnote referring to the documentation of sleep disturbance due to night-time coughing. 4. A clarification was added that, at a minimum, the SpO2, feeding, respiratory muscle retractions, and respiratory rate should be evaluated on Day 1 before randomization, unless these assessments were already performed within the last 3 hours before randomization. 5. The method of stratified randomization per cohort was corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported