Clinical trial results:
A Phase I/IIa Multicentre Study in Otherwise Healthy Infants and Toddlers Hospitalised For and Diagnosed With Respiratory Syncytial Virus Lower Respiratory Tract Infection, Consisting of an Open-label Lead in Part Followed by a Double-blind, Placebo-controlled Part, to Evaluate the Safety, Tolerability, and Clinical Activity of ALX-0171, Administered Via Inhalation, in Addition to Standard of Care

Summary

EudraCT number	2014-002841-23
Trial protocol	GB HU SK BE ES EE LV BG PL
Global end of trial date	17 February 2016

Results information

Result version number	v1 (current)
This version publication date	18 August 2016
First version publication date	18 August 2016

Trial information

Trial identification

Sponsor protocol code	ALX0171-C104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02309320
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ablynx
Sponsor organisation address	Technologiepark 21, Zwijnaarde, Belgium, 9052
Public contact	clinicaltrials@ablynx.com, Ablynx NV, +32 (0)9 262 0000, clinicaltrials@ablynx.com
Scientific contact	clinicaltrials@ablynx.com, Ablynx NV, +32 (0)9 262 0000, 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	17 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2016
Global end of trial reached?	Yes
Global end of trial date	17 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and tolerability of multiple doses of ALX-0171

Protection of trial subjects:

Only subjects who met all the study inclusion and none of the exclusion criteria were to be randomized to trial treatment. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Randomized patients were required to stay in the hospital during the treatment period.
The Investigator informed each subject's parent(s) or legal guardian(s) of the nature of the study (objectives, methods, potential hazards and benefits, and any discomfort that subjects might have during participation in the study) and the procedures involved, using the information in the main ICF. After given sufficient time to understand the information and to ask questions, subject's parent(s) or legal guardian(s) provided written informed consent before enrolment of their child in this study and before any protocol specified procedures were performed. No additional safety evaluations requiring additional consent procedures have become necessary in this study.
If this was not standard practice at the site, an additional short ICF could be signed by the subject's parent(s)/legal guardian for performing a Sponsor-provided respiratory syncytial virus (RSV) diagnostic test.

Background therapy:

The standard of care during hospitalization for RSV LRTI, as defined for this study, included (but was not limited to) the following:

- Oxygen supplementation (via simple face mask up to 6 L/min, nasal cannula up to 2 L/min, or headbox oxygen)
- Fluid/food supplementation (administered intravenously or via nasogastric tube, if applicable)
- Short-acting β2 agonists
- Antibiotics (in case of secondary bacterial infection [superinfection] during hospitalization)
- Epinephrine (but not within 1 hour before study drug administration)
- Anticholinergics
- Antipyretics and/or nonsteroidal anti inflammatory medication

The treatment and care provided to each subject were determined by the Investigator (or designee) according to institutional practice. The recommendations on the diagnosis and management of bronchiolitis in subjects under 2 years of age, as described by the American Academy of Pediatrics (2006), could be followed in addition to the institutional practice.

Other concomitant medications were allowed, apart from those listed under the prohibited therapies (see below), at the Investigator's discretion (based on medical need).

The following treatments were prohibited during the study:

- Ribavirin
- Hypertonic saline
- Heliox
- Leukotriene receptor antagonists (e.g., montelukast)
- Exogenous surfactant
- Corticosteroids
- Mucolytics
- Ventilation other than oxygen supplementation via simple face mask, nasal cannula, or headbox

- Intravenous immunoglobulin and palivizumab (subjects who required RSV prophylaxis were not eligible for inclusion in the study)

After the end of the study, each subject was to be treated according to standard clinical practice.

Evidence for comparator: -	
Actual start date of recruitment	19 December 2014
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	Israel: 7
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Hungary: 5
Worldwide total number of subjects	51
EEA total number of subjects	28

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)	51
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:

Subjects were enrolled in 27 study centers in Asia (Malaysia, Philippines, Thailand and Israel) and in Europe (Belgium, Bulgaria, Hungary, Poland, Slovakia, Spain and the United Kingdom) between 18 Dec 2014 and 17 Feb 2016. The study started with an open-label lead-in part (5 subjects) and was then continued double-blind.

Pre-assignment

Screening details:

- 57 subj screened, 53 randomized, 51 completed study visits (Safety population)
- 1 subj discontinued due to a SAE before receiving study drug (excl. from Safety population)
- 1 subj discontinued from the study prior to dosing on Day 3 (withdrawal consent)
- 1 subj did not receive study drug (protocol violation - excl. from Safety population)

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, Data analyst, Carer, Assessor

Blinding implementation details:

The study started with an open-label lead-in part: 5 subjects received ALX-0171. After positive recommendation of the DMC, the remainder of the study was double-blind. All subject's parent(s)/legal guardian(s), Investigators (+ designees) and all study personnel involved in the study were blinded to treatment assignment. One unblinded, independent statistician was assigned to prepare summaries for the DMC members but did not otherwise participate in the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	ALX-0171

Arm description:

A total of 51 subjects completed the study visits: 35 subjects received ALX-0171 and 16 subjects received placebo in the study, 32 subjects completed study treatment in the ALX-0171 arm, all subjects completed study treatment in the placebo arm.

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

Dosage and administration details:

Eligible subjects received ALX-0171 (open-label lead in part, 5 subjects) or were randomly assigned to receive ALX-0171 via inhalation with a FOX Flamingo Inhalation System once daily for 3 consecutive days. The dose administered was based on body weight.

Study drug was administered following a 2-hour baseline monitoring period and administration of the short-acting β2-agonist salbutamol.

Arm title	Placebo

Arm description:

A total of 51 subjects completed the study visits: 35 subjects received ALX-0171 and 16 subjects received placebo in the study, 32 subjects completed study treatment in the ALX-0171 arm, all subjects completed study treatment in the placebo arm.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Eligible subjects were randomly assigned to receive placebo (after open-label lead-in part) via inhalation with a FOX Flamingo Inhalation System once daily for 3 consecutive days.

Study drug was administered following a 2 hour baseline monitoring period and administration of the short-acting β2-agonist salbutamol.

Number of subjects in period 1	ALX-0171	Placebo
Started	35	16
Completed	32	16
Not completed	3	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	ALX-0171
Reporting group description:	
A total of 51 subjects completed the study visits: 35 subjects received ALX-0171 and 16 subjects received placebo in the study, 32 subjects completed study treatment in the ALX-0171 arm, all subjects completed study treatment in the placebo arm.	
Reporting group title	Placebo
Reporting group description:	
A total of 51 subjects completed the study visits: 35 subjects received ALX-0171 and 16 subjects received placebo in the study, 32 subjects completed study treatment in the ALX-0171 arm, all subjects completed study treatment in the placebo arm.	

Reporting group values	ALX-0171	Placebo	Total
Number of subjects	35	16	51
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	35	16	51
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: months			
arithmetic mean	7.76	8.17	
standard deviation	± 5.561	± 6.052	-
Gender categorical			
Units: Subjects			
Female	9	6	15
Male	26	10	36

End points

End points reporting groups

Reporting group title	ALX-0171

Reporting group description:

A total of 51 subjects completed the study visits: 35 subjects received ALX-0171 and 16 subjects received placebo in the study, 32 subjects completed study treatment in the ALX-0171 arm, all subjects completed study treatment in the placebo arm.

Reporting group title	Placebo

Reporting group description:

A total of 51 subjects completed the study visits: 35 subjects received ALX-0171 and 16 subjects received placebo in the study, 32 subjects completed study treatment in the ALX-0171 arm, all subjects completed study treatment in the placebo arm.

Primary: 1. Subjects with treatment-emergent adverse events (TEAEs)

End point title	1. Subjects with treatment-emergent adverse events (TEAEs)[1]

End point description:

The summary table for the treatment-emergent adverse events is presented (safety population). One subject experienced 2 severe non-treatment related TEAEs (hypotonia and hyporesponsiveness). The events were considered serious.

End point type	Primary

End point timeframe:

From screening until last follow-up visit

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only number of subjects with TEAEs are provided

End point values	ALX-0171	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[2]	16[3]		
Units: number of subjects with TEAEs				
Subjects w AEs leading to death	0	0		
Subjects w SAEs	4	0		
Subjects w AEs leading to treatm discontinuation	2	0		
Subjects w AEs leading to withdrawal	0	0		
Subjects w severe TEAEs	1	0		
Subjects w possibly rel. TEAEs (judged by invest)	3	0		
Possibly related TEAE: cough	1	0		
Possibly related TEAE: rhinorrhea	1	0		
Possibly related TEAE: pyrexia	1	0		

Notes:

[2] - safety population

[3] - safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 2. Immunogenicity

End point title	2. Immunogenicity

End point description:

The number of subjects with treatment-emergent anti-drug antibodies is presented.

End point type	Secondary

End point timeframe:

at Day 14

End point values	ALX-0171	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[4]	16[5]		
Units: Subjects	8	1		

Notes:

[4] - safety population

[5] - safety population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 3. Viral loads from nasal swabs

End point title	3. Viral loads from nasal swabs

End point description:

Data on mean viral loads in the course of the study are presented (plague assay).
The first ALX-0171 dose reduced mean cultivatable virus titers to below the quantification limit within 6 hours which was not the case for placebo treated subjects (mean change from baseline of 0.879 log10 PFUs/mL for ALX-0171 versus -0.434 log10 PFUs/mL for placebo following the first dose) although baseline values were lower in the ALX-0171 group than in the placebo group. Subsequent mean cultivatable virus titers were maintained below the quantification limit in the ALX-0171 treated subjects whereas for subjects in the placebo group, mean cultivatable virus titers only dropped below the quantification limit after the second dose. For these samples a numerical value half the lower limit of quantification (LLOQ) was imputed.

End point type	Other pre-specified

End point timeframe:

Day 1: pre-dose, post-dose
Day 2, Day 3: pre-dose
at discharge

End point values	ALX-0171	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[6]	16[7]		
Units: log10 PFU/mL				
arithmetic mean (standard deviation)				
Day 1, 2 h pre-dose	2.047 (± 1.4702)	2.396 (± 1.4651)		
Day 1, 6 h post-dose	1.159 (± 0.8861)	1.962 (± 1.2688)		
Day 2, 2 h pre-dose	1.189 (± 0.8813)	1.768 (± 1.0745)		

Day 3, 2 h pre-dose	1.14 (± 0.8238)	1.261 (± 0.8087)		
at discharge	0.957 (± 0.4649)	1.109 (± 0.7186)		

Notes:

[6] - safety population (not all data available for all subjects at all time points)

[7] - safety population

Statistical analyses

No statistical analyses for this end point

Post-hoc: 4. Global severity score (GSS)

End point title	4. Global severity score (GSS)

End point description:

A post-hoc analysis was performed to assess comprehensively the collected clinical activity data which resulted in the Global Severity Score (GSS). The GSS is derived from the ReSVinet scale which is a validated clinical scoring system that allows objective categorization of infants with respiratory infections based on feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnea, general condition, fever. A decrease in the GSS indicates an improvement.
Mean GSS scores are presented at different time points for the modified safety population, excluding the 5 subjects participating to the open-label part of the study and excluding 5 subjects without detectable RSV.
The resulting GSS showed decreases in mean scores over the course of the study for both treatment groups with improvements being more pronounced in the ALX-0171 group compared to the placebo group starting at Day 1, which suggested faster recovery with ALX-0171 treatment versus placebo.

End point type	Post-hoc

End point timeframe:

Day 1: 2 h pre-dose, 6 h post-dose
Day 2: 2 h pre-dose, 6 h post-dose
Day 3: 2 h pre-dose, 6 h post-dose

End point values	ALX-0171	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[8]	15[9]		
Units: Global Severity Score				
arithmetic mean (standard deviation)				
Day 1, 2 h pre-dose	7.7 (± 2.42)	7.4 (± 3.2)		
Day 1, 6 h post-dose	5.8 (± 3.27)	6.5 (± 4.03)		
Day 2, 2 h pre-dose	5.1 (± 2.77)	6.4 (± 2.97)		
Day 2, 6 h post-dose	4.4 (± 2.94)	6.1 (± 3.63)		
Day 3, 2 h pre-dose	3.5 (± 2.3)	4.3 (± 3.33)		
Day 3, 6 h post-dose	3.2 (± 2.11)	3.8 (± 3.13)		

Notes:

[8] - Modified safety population

[9] - Modified safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening until last follow-up visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	ALX-0171
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	ALX-0171	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 35 (11.43%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Hyporesponsive to stimuli			
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ALX-0171	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 35 (31.43%)	4 / 16 (25.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Crying			
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	2 / 35 (5.71%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 35 (2.86%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Rash maculo-papular			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2014	Protocol version 2.0: (The initial version of the protocol, Protocol version 1.0 was not submitted due to an administrative error in the Schedule of Assessments.) A minor correction was included in the Schedule of Assessments (timing of nasal swab assessments) prior to initiating the clinical trial applications.
23 December 2014	Protocol v3.0: The inclusion criterion that specified the duration of symptoms prior to screening was updated to include subjects with appearance of symptoms that are likely related to respiratory syncytial virus infection within ≤ 7 days (instead of ≤ 4 days) at the time of screening, based on the Investigator's judgement. The age of inclusion for the double-blind, placebo controlled part of the trial was updated from 5 months to potentially 3 months, dependent on a positive recommendation from the independent data monitoring committee after completion of Part A. These changes were included to increase Protocol flexibility with regards to recruitment. Other minor clarifications and updates were incorporated as well.
11 August 2015	Protocol v4.0: The age of inclusion for the double blind, placebo controlled part of the trial was updated from 3 months to potentially 28 days, dependent on a positive recommendation from the independent data monitoring committee (after 15 subjects had completed study treatment in Part B). The design of the study was updated: once all subjects in Part B had completed the study drug treatment period, up to 18 additional subjects aged 28 days to < 5 months were to be enrolled in an expansion cohort (Part C). These changes were included to allow the Sponsor to obtain additional data in an extended and highly relevant population. Other minor clarifications and updates were incorporated as well.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This First-in-Infant trial was primarily focused on safety and tolerability and no formal statistical analysis was prespecified.

Notes: