Ablynx

Nanobodies®
creating better medicines

Results from the first-in-infant Phase I/IIa study with the anti-RSV Nanobody, ALX-0171

3 May 2016

ALX-0171 – Phase I/IIa study results

Participants on the call

Dr Edwin Moses

CEO

Dr Robert K. Zeldin

CMO

Dr Antonin de Fougerolles

CSO

Inhaled anti-RSV Nanobody – ALX-0171

Potential breakthrough for the treatment of RSV infections

- **Innovative, wholly-owned** product, based on Ablynx's unique Nanobody® technology
- Biological drug delivered by **inhalation – major platform advantage**
- **Most advanced** product in clinical development to **treat** RSV infections in infants
- **Critical** pre-clinical and clinical **milestones achieved**
- **Next Phase II study** in infants being planned

RSV infection in infants

Leading cause of infant hospitalisation

Evolves to distressing symptoms

Symptomatic treatment

8-20% hospitalised

- Seasonal disease with no specific therapeutic drug treatment available
- 60%-70% of children will have been infected by the age of 1 year[1]
- >3 million children (<5 years) hospitalised worldwide each year[1]
- 3,000-8,500 deaths in infants <2 years globally p.a.[2]
- Long-term disease burden
  - increased medical cost in the first year following RSV infection[3]
  - associated with prolonged wheezing and increased risk of asthma development[4]

High unmet need for an effective therapeutic

[1]Nair *et al*, Lancet 2010; [2] Byington *et al,* Pediatrics 2014; [3] Shi *et al*, J Med Econ, 2011; [4] Sigurs *et al*, Thorax, 2010; Backman *et al*, Acta Pediatr, 2014

Inhaled anti-RSV Nanobody – ALX-0171

Robust trivalent Nanobody product

- Trivalency improves potency and strain coverage[1]
  - 7,000 fold increase in potency over monovalent construct
  - 10,000 fold reduction in viral titres *in vitro*
  - Neutralises* 87% of a chosen set of clinical RSV isolates as compared to only 18% for Synagis® (pavilizumab)

- Robustness of the Nanobody allows efficacy to be maintained after nebulisation[2]

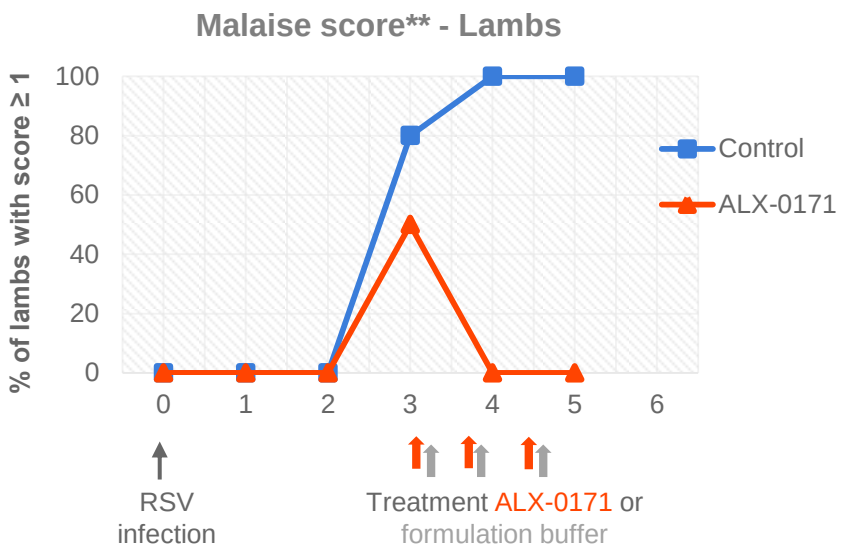
* to below the limit of detection

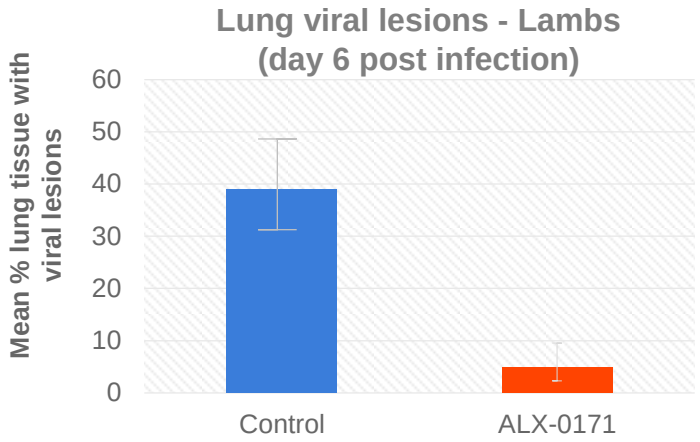
[1] Human antibodies conference April 2014 [2] RDD conference May 2015

Inhaled ALX-0171

Strong therapeutic effect demonstrated *in vivo*

- Strong therapeutic effect* following daily inhalation for 3 consecutive days in neonatal lamb model for infant RSV





* RSV Symposium November 2014

** Composite assessment of disease related parameters such as weakness, depression, lethargy, drooping of ears and not eating

Inhaled ALX-0171

Successfully completed 3 Phase I inhalation studies in adults

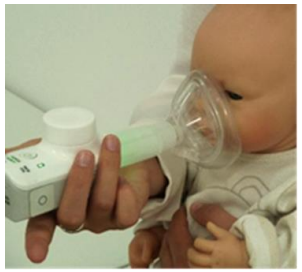
	Number of subjects	Dose SAD and MAD	Outcome
First-in-human study	60	2x/day for 5 days	Well-tolerated, no clinically relevant adverse events or effects on lung function
Safety study in adults with hyper-reactive airways	24	daily for 5 days	Some cases of mild bronchoconstriction which could be immediately reversed
PK study	41	daily for 5 days and single *iv* dose	Local half-life of ALX-0171 is ~20 hours confirming potential for once-daily dosing

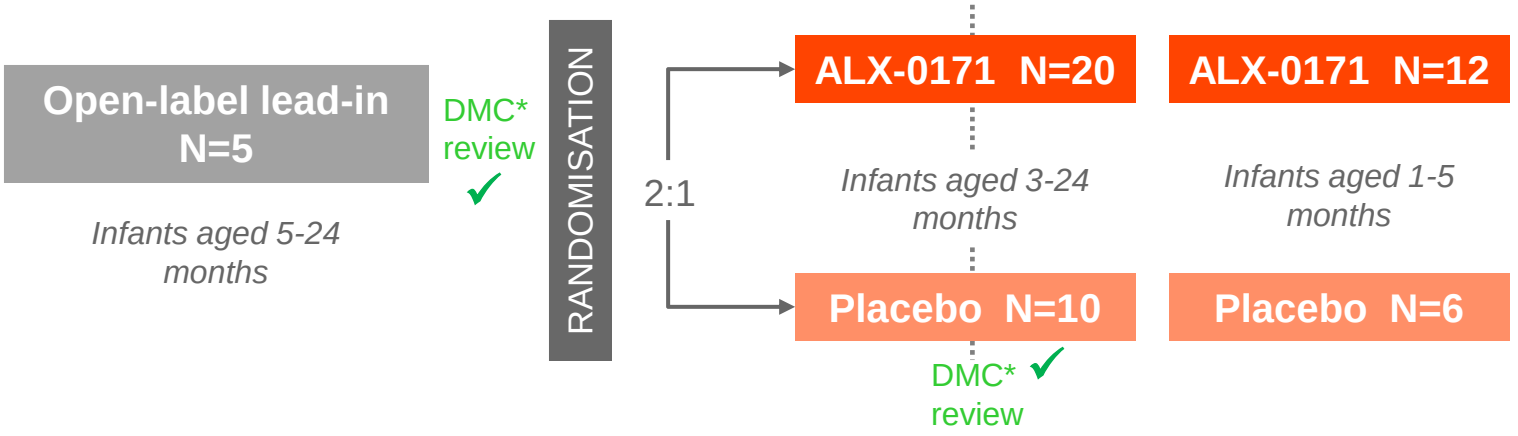
Inhaled ALX-0171 administered safely to >100 adults

Inhaled ALX-0171

Phase I/IIa study in 53 hospitalised RSV-infected children

- Recruitment from Q4 2014 to Q1 2016
- Study centres in Europe and Asia-Pacific region
- Adapted infant inhalation device (vibrating mesh)
- Inhaled ALX-0171 administered once/day, for 3 consecutive days





Primary endpoint:
Safety and tolerability of ALX-0171

Secondary endpoints:
Assessment of clinical effect (feeding, respiratory rate, O_2 saturation, wheezing, coughing, general appearance), PD, PK and immunogenicity

* Data monitoring committee

First-in-infant Phase I/IIa study

Baseline characteristics – balanced within randomised groups

	Open-label group ALX-0171	Randomised group ALX-0171	Randomised group Placebo
Number of subjects randomised	5	32	16
Number (%) of subjects in the safety population (who received at least one dose)	5 (100)	30*	16
Mean age (months)	7.1	7.9	8.2
Males (%)	4 (80.0)	22 (73.3)	10 (62.5)
Mean weight (kg)	8.0	7.4	7.7
Mean number of days between onset of symptoms and screening	3.4	3.9	3.8
Mean Global Severity Score** (day 1, predose)	10.0	7.3	7.3

* 2 subjects discontinued between randomisation and dosing

** a composite score reflecting an assessment of feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnoea, general condition and fever

First-in-infant Phase I/IIa study

Safety and tolerability

	Open-label group ALX-0171 (N=5)	Randomised group ALX-0171 (N=30)	Randomised group Placebo (N=16)
Adverse events (AEs)			
- number (%) of subjects with an AE	4 (80.0)	9 (30.0)	4 (25.0)
- number (%) of subjects with a treatment-related AE	1 (20.0)	2 (6.7)	0 (0.0)
Serious adverse events (SAEs)			
- number (%) of subjects with an SAE	3* (60.0)	1** (3.3)	0 (0.0)
- number (%) of subjects with treatment-related SAEs	0 (0.0)	0 (0.0)	0 (0.0)

* 1 of whom discontinued ** subject discontinued

Study primary endpoint achieved

Safety and tolerability profile confirmed in the target population

First-in-infant Phase I/IIa study

PK and immunogenicity

- Pharmacokinetics (PK)
  - ALX-0171 detected in serum samples 6 hours after the last dose
  - consistent with lung exposure

- At follow-up visit, treatment-emergent anti-drug antibodies were detected in 23% of patients, consistent with general immune activation in the lungs due to the RSV infection
  - no relation seen with adverse events
  - no apparent effect on PK

First-in-infant Phase I/IIa study

Anti-viral effect explored using nasal swabs

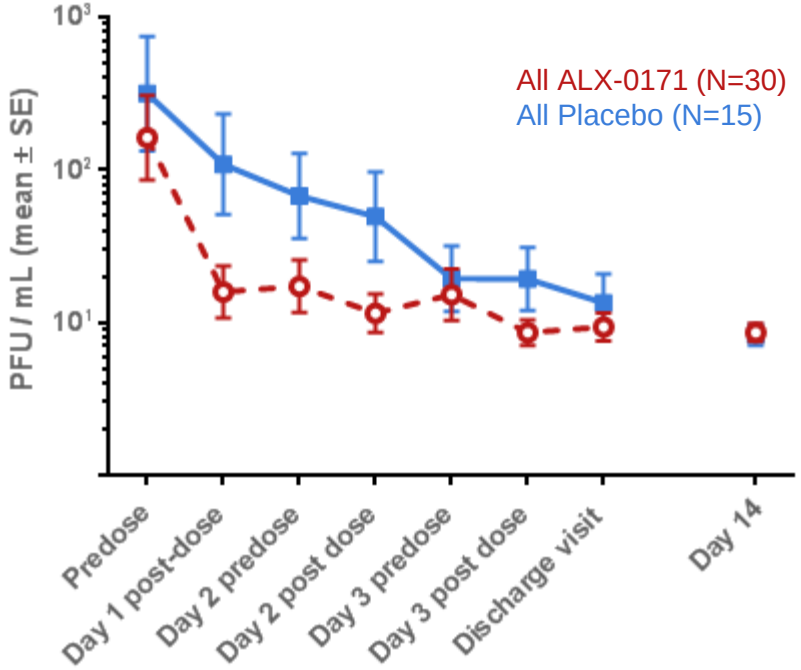
- 2 methods used to measure anti-viral effect
  - qRT-PCR: measuring all viral RNA
  - plaque assay: measuring infectious virus
- 2 outcomes per method
  - viral load over time (nasal swabs taken prior to dosing and 6 hours after)
  - time to undetectable virus: measures the time from start of treatment until the time of the first undetectable viral titre in 2 consecutive nasal swabs
- Study population (open-label, lead-in group and double-blind, randomised treatment group)
  - ALX-0171: N=30 (excludes 4 subjects* with unconfirmed RSV infection; and 1 with no result)
  - placebo: N=15 (excludes 1 subject* with unconfirmed RSV infection)

* No evidence for RSV infection by plaque or qRT-PCR assay at any time during the study; presumed false positives from rapid diagnostic strip test

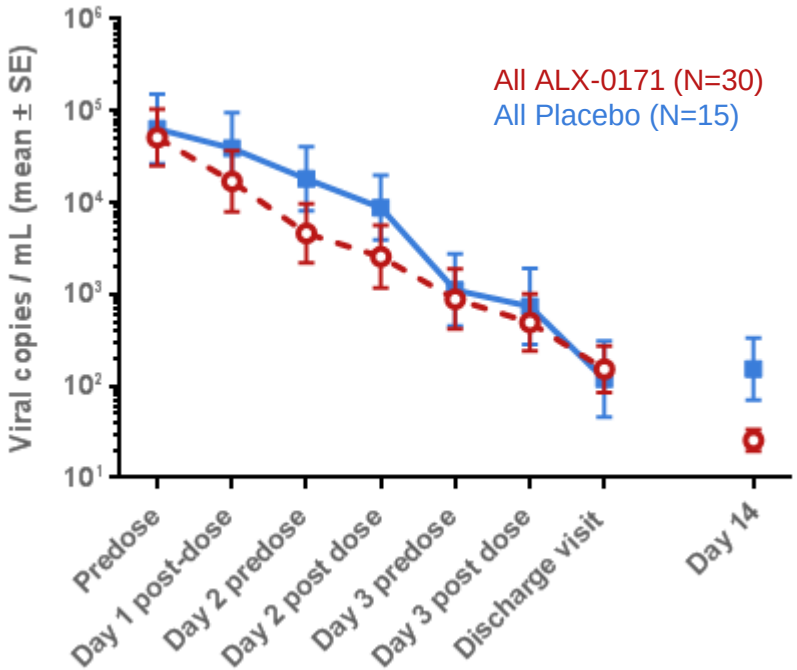
First-in-infant Phase I/IIa study

Anti-viral effect – viral load over time

plaque assay



qRT-PCR

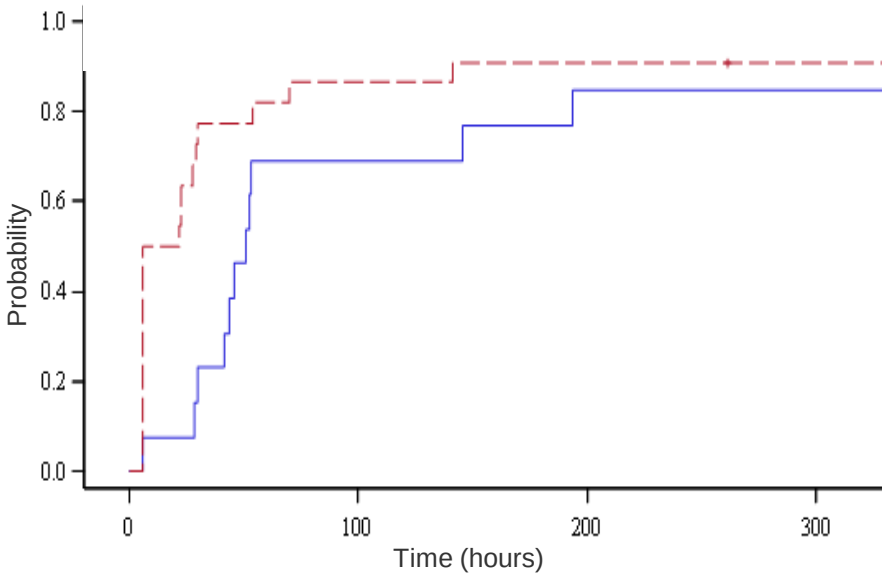


Treatment with ALX-0171 had an immediate impact on viral replication in RSV-infected infants

First-in-infant Phase I/IIa study

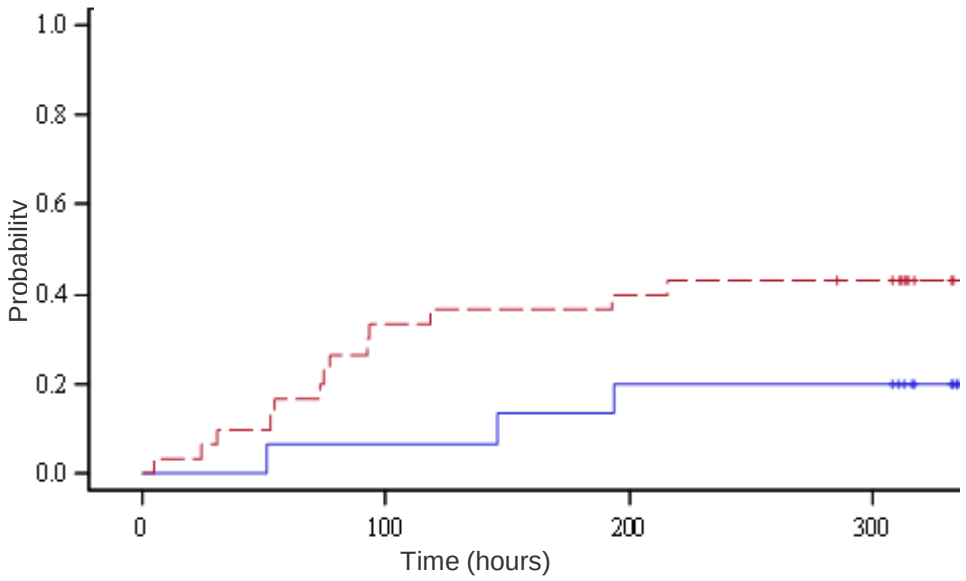
Anti-viral effect – time to undetectable virus

plaque assay



All ALX-0171 (N=22)
All Placebo (N=13)

qRT-PCR



All ALX-0171 (N=30)
All Placebo (N=15)

Treatment with ALX-0171 resulted in an anti-viral effect in RSV-infected infants

These study populations also exclude subjects who had undetectable virus/viral RNA in the assay used, both at baseline and at the first post-dose time point

First-in-infant Phase I/IIa study

Clinical effect

- Post-hoc assessment of clinical effect based on the Global Severity Score*
  - clinical score (up to 20 points) that allows categorisation of infants with respiratory infections on 7 different parameters:
    - feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnoea, general condition and fever

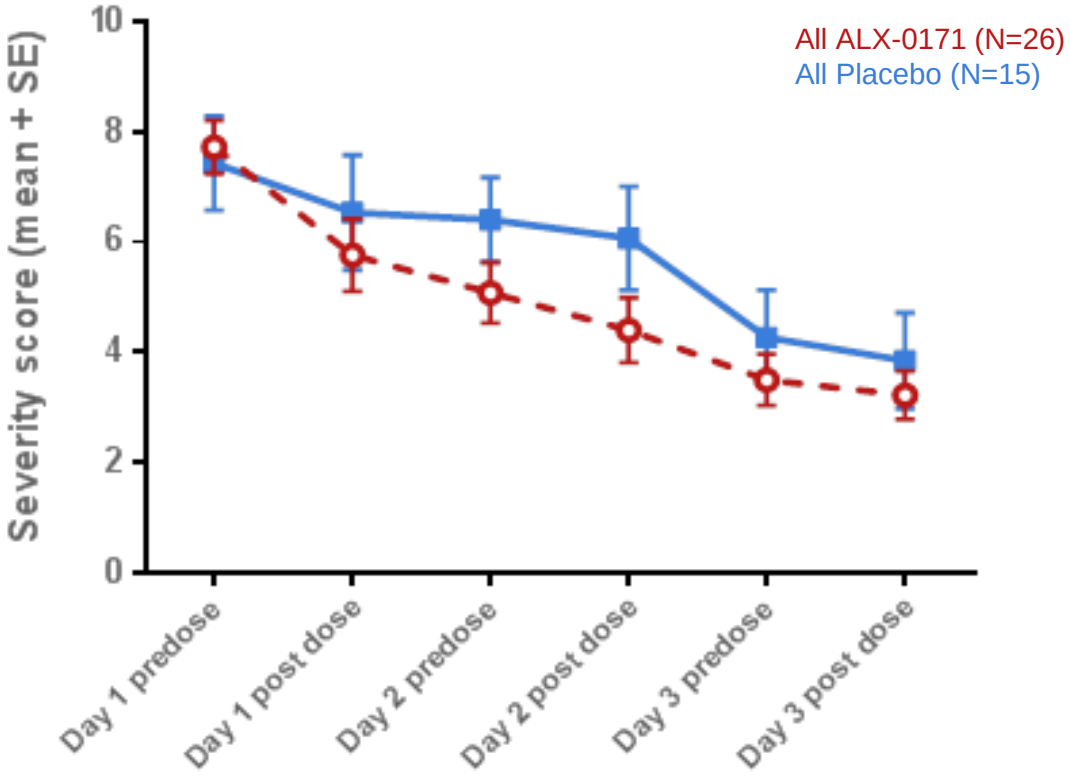
- Study population: double-blind, randomised treatment group
  - ALX-0171: N=26 (excludes 4 subjects** with unconfirmed RSV infection)
  - Placebo: N=15 (excludes 1 subject** with unconfirmed RSV infection)

* Poster presentation, Justicia *et al*: "Development and validation of a new clinical scale for infants suffering from acute respiratory infection"

** No evidence for RSV infection by plaque or qRT-PCR assay at any time during the study; presumed false positives with diagnostic test

First-in-infant Phase I/IIa study

Overall disease severity assessment – Global Severity Score*



* Overall disease severity assessment including feeding intolerance, medical intervention, respiratory difficulty, respiratory frequency, apnoea, general condition and fever

Encouraging initial indication of therapeutic effect

Inhaled ALX-0171

Potential breakthrough for the treatment of RSV infections

- Direct delivery to the site of infection through inhalation

- No treatment-related serious adverse events
- Good safety and tolerability profile confirmed
- Anti-drug antibodies did not have an apparent effect on PK and no apparent relation to adverse events

- Demonstrated anti-viral effect and showed encouraging trends in Global Severity Score in infants (aged 1-24 months) who were hospitalised with an RSV infection

Results from the first-in-infant Phase I/IIa study support advancement to a Phase II efficacy study in infants