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

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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

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

High unmet need for an effective therapeutic

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 \textit{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

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* 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

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

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

**Randomisation**

Open-label lead-in

- Infants aged 5-24 months
- N=5

2:1

ALX-0171 N=20

Infants aged 3-24 months

DMC* review

ALX-0171 N=12

Infants aged 1-5 months

DMC* review

Placebo N=10

Placebo N=6

* Data monitoring committee
## First-in-infant Phase I/IIa study

### Baseline characteristics – balanced within randomised groups

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

* 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

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

* 1 of whom discontinued  
** subject discontinued

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**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

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

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