ALX-0171: safety, efficacy and therapeutic potential of an inhaled anti-RSV Nanobody

Erik Depla
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# Ablynx

## Corporate snapshot

### CORPORATE
- Drug discovery and development company in Ghent, Belgium
- >300 employees

### TECHNOLOGY
- Pioneer in next generation biological drugs – Nanobodies®
- >500 granted and pending patents

### PRODUCTS
- >30 programmes – six at the clinical development stage
- Three clinical proof-of-concepts (POC)
- 2 wholly-owned products in later stage clinical development (Phase III & Phase II)
- >10 new clinical programmes anticipated over the next 3 years

### PARTNERS
- AbbVie, Boehringer Ingelheim, Eddingpharm, Merck & Co, Merck Serono and Novartis

### FINANCIALS
- €206M in cash at December 31st 2014
Nanobodies

Derived from heavy-chain only antibodies

- *Camelid* heavy-chain only antibodies are stable and fully functional
- Nanobodies represent the next generation of antibody-derived biologics

![Conventional antibodies](image1)

![Heavy chain only antibodies](image2)

Ablynx’s Nanobody

- small
- robust
- sequence homology comparable to humanised/human mAbs
- easily linked together
- nano- to picomolar affinities
- intractable targets
- multiple administration routes
- manufacturing in microbial cells
Ablynx’s platform

Rapid generation of high quality biologics

Immunise llamas with antigen or use synthetic library

Wide range of highly diverse Nanobodies with 0.1-10nM affinities

Formatted* Nanobodies ready for *in vivo* testing

Cloning and production in microbial systems

~12-18 months

*Glycine-serine linkers from C-terminus to N-terminus
## Nanobody platform

### Competitive advantages

<table>
<thead>
<tr>
<th>Mix and match</th>
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<tr>
<td>Targeting different pathways at once with a single Nanobody construct, e.g. multiple checkpoint inhibitors</td>
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<thead>
<tr>
<th>Alternative delivery routes</th>
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<tbody>
<tr>
<td>Inhalation</td>
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<tr>
<td>Needle-free</td>
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<td>Oral-to-topical</td>
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<td>Ocular</td>
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<th>Customised half-life extension</th>
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<tr>
<td>Weeks/days/hours</td>
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<tr>
<td>Fc</td>
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<tr>
<td>Albumin-binding Nanobody</td>
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<th>Challenging and intractable targets</th>
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<tr>
<td>Nanobodies against ion channels and GPCRs</td>
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<td>Nanobodies can reach conserved cryptic epitopes</td>
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<tr>
<th>Cell killing</th>
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<tr>
<td>Nanobody-drug conjugates</td>
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<tr>
<td>Ag-1</td>
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<td>Ag-1</td>
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<td>Ag-1</td>
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<th>Cell- /tissue-homing</th>
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<tr>
<td>Cell specificity</td>
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<td>Immune cell recruitment</td>
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<td>Tissue-specific targeting</td>
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<tr>
<th>Manufacturing</th>
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<tr>
<td>High-yield, high-concentration, low-viscosity, microbial production</td>
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Infant Respiratory Syncytial Virus infection

High unmet medical need

• Leading cause of infant hospitalisation and primary viral cause of infant death
  – ~300,000 children* (< 5 years) hospitalised per year in 7 major markets\(^1,2\)
  – 1.9 million outpatient visits per year for infants under 1 year of age
  – increased medical cost in the first year following RSV infection\(^3\)
  – prolonged wheezing and increased risk for asthma development\(^4\)

• No widely accepted drug available to treat RSV infections
  – Synagis\(^\circledR\) used as prophylaxis in high-risk and/or pre-term infants only

* Extrapolation based on estimated US prevalence
Respiratory Syncytial Virus (RSV)

Generation of Nanobodies to the F-protein

- Glycoprotein F trimer
  - essential for viral entry/fusion of viral and host membranes
  - highly conserved
  - several neutralisable regions / epitopes

RSV F-protein (pre-fusion)

McLellan et al. 2013 Science
Anti-RSV Nanobody ALX-0171

Multi-valent formatting to improve potency

- Tri-valent anti-RSV (ALX-0171)
  - improve activity and strain coverage by multi-valency
  - superior virus neutralisation as compared to palivizumab
# Anti-RSV Nanobody ALX-0171

## Increased potent strain coverage

- Tri-valent anti-RSV (ALX-0171)
  - 5-fold more clinical isolates neutralised below LLOD with ALX-0171 compared with palivizumab (equal concentration of both compounds)

<table>
<thead>
<tr>
<th></th>
<th>A-strain</th>
<th>B-strain</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>29</td>
<td>61</td>
</tr>
<tr>
<td>palivizumab</td>
<td>0 (0%)</td>
<td>11 (38%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>ALX-0171</td>
<td>30 (94%)</td>
<td>23 (79%)</td>
<td>53 (87%)</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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Number of strains neutralised below LLOD

**Increased neutralisation capacity against a broad panel of RSV isolates**
Delivery to the site of infection

Nanobody advantage for nebulisation

• RSV replicates exclusively at the apical site of the respiratory tract → nebulisation is the optimal route to ensure fast delivery of ALX-0171
• ALX-0171 nebulisation:
  – using nebuliser with vibrating mesh technology: small, silent and rapid
  – ≥ 95% of filled volume nebulised
  – no significant molecular changes and no potency loss

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALX-0171 Release Specification a</th>
<th>ALX-0171 post-nebulisation b</th>
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<tbody>
<tr>
<td>Appearance</td>
<td>Free of visible particles</td>
<td>Free of visible particles</td>
</tr>
</tbody>
</table>
| Content | • OD280: 50 ± 10 mg/ml
• Absorbance at 340 nm | • 46.7 mg/ml
• 0.000 |
| SE-HPLC | • ≥ 85% main peak
• ≤ 5% HMW | • ≥ 97% main peak
• ≤ 2% HMW |
| Potency | 100 ± 50% compared to reference | 111% |
| NGI c | | MMAD: 4.22 µm (GSD 1.58) |

a For clinical Phase I/II material.
b Results after nebulisation of ALX-0171 GMP Drug Product upon 36 months storage at long-term storage conditions (5°C ± 3°C).
c NGI measurement performed at release.

HMW: product-related high-molecular weight variants, NGI: Next Generation Impactor, MMAD: mass median aerodynamic diameter; GSD: Geometric Standard Deviation
Device development throughout the project

Customised infant inhalation device

• Lamb studies
  – vibrating mesh: ≈3 µm particles for smaller airways
  – nasal inhalation (cone)

• Phase 1: three studies in adults
  – Akita² Apixneb (oral inhalation, breath-actuated)
  – vibrating mesh: ≈4 µm particles
  – established large safety window: maximal lung deposition

• First-in-infant study: hospitalised infants
  – customised CE-marked FOX-Flamingo inhalation system
  – design supported by handling study
  – battery operated hand-held device
  – vibrating mesh: ≈3 µm particles
  – nasal inhalation (soft face mask)
  – continuous air or O₂ supply during treatment
Neonatal lamb model*

*In vivo* study design

- Lambs develop lower respiratory tract infection which is associated with general malaise and specific lung pathology (comparable to infants)
- Treatment at peak of viral load on day 3 post infection (symptoms and lung pathology are already clearly present)
- Lambs develop clinical symptoms such as wheezing (comparable to infants)

*Mark Ackerman, Iowa State University
**ALX-0171 in vivo study**

*Proof-of-concept achieved in neonatal lambs*

**Mean viral titers in BALF**
- (day 6 post infection)

**IHC scores viral F protein expression**
- (day 6 post infection)

**ALX-0171 treatment results in**
- strong reduction of viral titres in bronchoalveolar lavage fluid (BAL)
  - coincides with strong reduction F protein expression
- strong reduction of gross viral lung lesions (% involved lung tissue)
- a clear effect on general health status
  - weakness, depression, lethargy, drooping of ears, not eating
ALX-0171 *in vivo* study

**Effect on viral lung lesions**

- Plum red RSV lesions seen in lungs of RSV-infected lambs on day 6 post-infection
  - present on all lung lobes assessed

Daily inhalation of ALX-0171 markedly reduced gross lung viral lesions
ALX-0171 *in vivo* study

Strong effect on general health status of RSV-infected lambs

- Subjective scoring (0 to 4*) of parameters that measure general health
  - "Malaise" score: weakness, depression, lethargy, drooping of ears, and not eating

Daily inhalation of ALX-0171 markedly reduced symptoms of illness in RSV-infected neonatal lambs

- * 0 = no clinical signs; 4 = animals down
ALX-0171 – Phase I

Study design

- Determine safety and tolerability
- Evaluate lung function (spirometry and DLCO)
- Evaluate dose-limiting toxicity and determine maximum tolerated dose
- Evaluate PK (plasma)
- Evaluate immunogenicity (systemic and local)
ALX-0171 – Phase I

Study results

• Well-tolerated and no dose-limiting toxicity
  – no SAEs occurred
  – no trends and no dose-related TEAEs
  – no clinically significant findings or trends in clinical/laboratory parameters, vital signs, ECGs, physical examinations

• No clinically significant findings or trends in lung function
  – lung auscultations or lung function test parameters (spirometry and DLCO)
  – no trends in exhaled NO

• No treatment-emergent immunogenicity observed

• Opportunity for once daily dosing
  – estimate based on plasma PK: pulmonary average half-life of ≈ 20h
ALX-0171 – two additional Phase I inhalation studies in adults successfully completed

• Phase I safety study in adults with hyper-reactive airways
  – 24 subjects
  – single escalating doses ranging from 2 to 200 mg, as well as repeated daily inhalation of either 140 or 200 mg for 5 days
  – some cases of mild bronchoconstriction which could be immediately reversed

• Phase I PK study
  – 41 healthy volunteers
  – single dose and multiple dose of 200 mg inhaled daily for five days and single dose of 0.3 mg/kg i.v.
  – BALF, blood and urine sampling to allow full PK profiling
  – local half-life of ALX-0171 is approximately 20 hours, confirming potential for once-daily dosing
ALX-0171

Current status and next steps

- First-in-infant Phase IIa study initiated in Northern Hemisphere
  - lead-in phase successfully completed and confirmation to proceed with placebo-controlled phase of the study
  - preparations on-going to open clinical centres in the Southern Hemisphere and Asia

- Recruitment of Phase IIa study expected to be completed by end 2015 with results anticipated in H1 2016
ALX-0171 in development to treat RSV infection in infants

• Designed to be POTENT
  – high *in vitro* antiviral activity against recent clinical isolates
  – efficacy demonstrated in *in vivo* cotton rat and lamb model

• Designed with SAFETY in mind
  – biologic targeting the virus: intrinsic low risk for off-target effects
  – extensive preclinical package demonstrating good tolerability
  – well tolerated in human adult studies

• Designed for OPTIMAL DELIVERY
  – Nebulisation ➔ fast onset of action and high concentration at infection site

Potential as unique inhaled therapeutic to treat RSV infection in infants addressing a high unmet medical need
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The RSV core and project team
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