Non-clinical and early clinical development of Nanobodies: ALX-0171 example

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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

Heavy chain only antibodies

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

Mix and match
Targeting different pathways at once with a single Nanobody construct, e.g. multiple checkpoint inhibitors

Challenging and intractable targets
Nanobodies against ion channels and GPCRs
Nanobodies can reach conserved cryptic epitopes

Alternative delivery routes
- Inhalation
- Needle-free
- Oral-to-topical
- Ocular

Customised half-life extension
- Weeks/days/hours
- Fc
- Albumin-binding Nanobody

Cell killing
Nanobody-drug conjugates
- Ag-1
- Ag-1
- Ag-1

Cell- /tissue-homing
- Cell specificity
- Immune cell recruitment
- Tissue-specific targeting

Manufacturing
High-yield, high-concentration, low-viscosity, microbial production
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

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* 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

*Improved potency over 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>
</thead>
<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>
</tr>
</tbody>
</table>

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

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*

*Mark Ackerman, Iowa State University

**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)

*ONSET OF INFECTION*

*INOCULATION*

*Necropsy*

*Day 0*

**TREATMENT**
ALX-0171 *in vivo* study

**Proof-of-concept achieved in neonatal lambs**

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

- **Vehicle**
- **RSV Vehicle**
- **RSV ALX-0171**

**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 \textit{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

\begin{itemize}
  \item \textbf{Vehicle}
  \begin{itemize}
    \item Uninfected
    \item RSV-infected
  \end{itemize}
  \item \textbf{ALX-0171}
  \begin{itemize}
    \item Uninfected
    \item RSV-infected
  \end{itemize}
\end{itemize}

\textbf{Gross viral lesions}

\begin{itemize}
  \item Mean % involvement/lobe (\pm SE)
  \item \textbf{Vehicle}
  \item \textbf{ALX-0171}
  \item \textbf{RSV Vehicle}
  \item \textbf{RSV ALX-0171}
\end{itemize}

\textbf{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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Questions

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