Nanobodies® – creating better medicines

Jefferies 2014 Global Healthcare Conference
London – 19th November 2014

Dr Edwin Moses - CEO
Forward looking statements

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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)
- >10 new clinical programmes anticipated over the next 3 years

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

Financials
- >€200M in cash expected end 2014
Three-pronged business strategy

Fully-funded programmes with milestones and royalties

- approx. 20 programmes
- 5 discovery and 5 licensing deals
- >€285M in cash received
- Approximately €3bn in future milestones plus royalties

Co-discovery/co-development deals

- 3 co-co deals
- 3 programmes
- 50:50 ownership and option to convert into licensing deals
- >€50M in cash received

Wholly-owned product pipeline

- approximately 9 programmes
- aim to retain the optionality to partner if and when appropriate
## Pipeline of proprietary and partnered programmes

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Product name</th>
<th>Target</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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- **1st in class**
Unique technology

Nanobodies® - Inspired by nature
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

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’ 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

~12-18 months

* glycine-serine linkers from C-terminus to N-terminus
Ablynx’s unique biologics platform – competitive advantages

**Mix and match**

- e.g. targeting different checkpoint inhibitors with a single Nanobody construct

**Alternative delivery routes**

- Inhalation
- Needle-free
- Oral-to-topical
- Ocular

**Customised half-life extension**

- Weeks/days/hours
- Albumin-binding Nanobody
- Fc
- PEG

**Challenging and intractable targets**

- Nanobodies against ion channels and GPCRs
- Nanobodies can reach conserved cryptic epitopes

**Cell / tissue-homing**

- Cell specificity
- Immune cell retargeting
- Tissue-specific targeting

**Cell killing**

- Nanobody drug conjugates

- Ag-1
- Ag-2
Products in the clinic

Nanobodies® - Inspired by nature
## Leading programmes in the clinic

<table>
<thead>
<tr>
<th>Programme (target)</th>
<th>Indication</th>
<th>Key differentiating features</th>
<th>Stage</th>
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</table>
| **Caplacizumab** (vWF) | Thrombotic thrombocytopenic purpura | First-in-class orphan drug  
Novel mode of action  
Inhibition of microthrombi formation | Start Phase III mid-2015: results end 2017 |
| **ALX-0171** (RSV) | Respiratory syncytial virus infection           | First-in-class addressing high unmet need  
Inhaled Nb delivered to infection site  
Highly potent trivalent construct | Start POC infant study Q4 2014: results Q3 2015 |

### Proprietary

<table>
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<tr>
<th>Programme (target)</th>
<th>Indication</th>
<th>Partner</th>
<th>Key differentiating features</th>
<th>Stage</th>
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</thead>
</table>
| **ALX-0061** (IL-6R) | RA, SLE    | **abbvie** | Best-in-class opportunity  
Monovalent interaction; strong affinity and preferential binding to soluble IL-6R | Start Phase IIb/a (RA; SLE) in 2015  
RA results 2016 |
| **ALX-0761** (IL-17A/F) | Psoriasis   | **MERCK SERONQ** | Potent neutralisation of both IL-17A and IL-17F  
POC achieved in primate CIA* model | Phase Ib ongoing in psoriasis patients: results 2016 |

### Partnered

*Collagen induced arthritis model*
caplacizumab – anti-vWF

- First-in-class bivalent Nanobody with Orphan Drug Status
- Developed for the treatment of acquired thrombotic thrombocytopenic purpura (TTP)
- Phase III study to start in 2015
Acquired TTP – significant unmet medical need

Potentially life threatening rare disorder of the blood coagulation system
- incidence of 11.3 per million\(^2\)
- ~10,000 acute events annually in US and Europe

Extensive microscopic thrombi formed in small blood vessels throughout the body

High unmet medical need
- mortality remains high (10-20\%)\(^1\) and ~ 36\% of patients have relapses\(^2\)
- major morbidities after first TTP episode such as neurocognitive impairment
- no approved medicinal product for treatment available
- standard of care is plasma exchange (PEX) plus immune suppressants

\(^1\) Scully et al, Br J Haematology, 2012
\(^2\) George et al, 2008
Caplacizumab — prevents formation of microthrombi in TTP

Caplacizumab blocks the platelet – ULvWF interaction

Ex vivo assay for platelet string formation

Fluorescence microscopy image of platelets adhering to UL-vWF in plasma of TTP patients

Without treatment, fluorescently labelled platelets adhere to UL-vWF, observed as string-like structures

Caplacizumab inhibits the formation of platelet strings and potentially the associated microvascular thrombi in many organs
Caplacizumab – strong Phase II clinical proof-of-concept

Primary endpoint

• patients treated with caplacizumab achieved confirmed platelet normalisation at more than twice the rate of the group treated with placebo
• this effect was statistically significant (p = 0.013)

Secondary endpoint

• 71% less patients with an exacerbation
• 76% more patients in complete remission

Safety

• no deaths in the caplacizumab arm compared to 2 deaths in the placebo arm
• increased bleeding tendency, which is believed to be manageable
• overall, caplacizumab has an acceptable safety profile

In 2015, caplacizumab will be the first Nanobody to enter Phase III clinical development
ALX-0171 – anti-RSV

- First-in-class trivalent Nanobody for the treatment of respiratory syncytial virus (RSV) infection in infants
- Delivered through inhalation
- First-in-infant Phase IIa to start in Q4 2014
RSV infection in infants – 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\(^1,2\)
  - increased medical cost in the 1\(^{st}\) year following RSV infection\(^3\)
  - prolonged wheezing and risk for asthma development\(^4\)
  - ~3.5% mortality rate in hospitalised high-risk infants (~400 deaths/year in the US)

- No widely accepted drug available to treat RSV infections
  - Synagis\(^\text{®}\) used as prophylactic in high-risk pre-term infants only ($1.1bn sales in 2013)

* Extrapolation based on estimated US prevalence

ALX-0171 – neonatal RSV lamb model to assess efficacy

Study design – 5 animals per group

• mock-infected / ALX-0171 treated (vehicle)
• RSV infected / not treated
• RSV infected / ALX-0171 treated

Suitability of neonatal lamb model compared with human challenge model

- 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)
ALX-0171 – proof-of-concept achieved in RSV lamb model

Mean viral titers in BALF (day 6 post infection)

Log10 FFU/mL BAL

Vehicle | RSV Vehicle | RSV ALX-0171

Mean % Involvement (day 6 post infection)

Lung viral lesions

Vehicle | RSV Vehicle | RSV ALX-0171

% of lambs with score ≥ 1

RSV vehicle | RSV ALX-0171 | Vehicle

Daily inhalation of ALX-0171 for 3 consecutive days

• markedly reduced viral titres and lung lesions
• markedly reduced symptoms of illness
ALX-0171 – successful Phase I inhalation studies in adults

่า September 2012 – Phase I first-in-human study
  • 60 healthy volunteers
  • single–ascending dose and multiple dose up to 210 mg inhaled twice daily for 5 days
  • well tolerated, with no clinically relevant adverse events or effects on lung function

่าย May 2014 – Phase I safety study in adults with hyper-reactive airways
  • 24 subjects
  • single-ascending dose and multiple dose part up to 200 mg inhaled daily for five days
  • some cases of mild bronchoconstriction which could be immediately reversed

่าย May 2014 – Phase I PK study
  • 41 healthy volunteers
  • single and multiple dose of 200 mg inhaled daily for 5 days and single dose of 0.3 mg/kg iv
  • local half-life of ALX-0171 is approximately 20 hours, confirming potential for once-daily dosing
ALX-0171 – first-in-infant inhalation study

- Infants aged 5 to <24 months who are hospitalised for RSV infection
- 24 EU centres and additional centres Southern Hemisphere (risk mitigation)
- Custom-developed infant inhalation device (vibrating mesh)

Randomisation 2:1

- **ALX-0171** N=20
  - Inhaled ALX-0171 once/day or placebo
  - 3 consecutive days
- **Placebo** N=10
  - Open-label lead-in N=5
  - Inhaled ALX-0171 once/day
  - 3 consecutive days

**Review by DMC**

**Primary endpoint:**
Safety and tolerability of ALX-0171

**Secondary endpoints:**
Clinical effect (feeding, respiratory rate, wheezing, coughing, general appearance)
PD (viral load), PK (ALX-0171 systemic concentration) and immunogenicity

Start Q4 2014
Results expected H2 2015
ALX-0061 – anti-IL-6R

- Monovalent half-life extended Nanobody
- Best-in-class potential for the treatment of auto-immune disorders
- Global licensing agreement with AbbVie
- Phase IIb studies in RA and Phase IIa study in SLE to start in 2015
ALX-0061 – compelling Phase IIa results in RA patients

• Treatment was highly efficacious and was well tolerated at all doses
• No increase of adverse events upon extension of treatment
• No anti-drugs antibodies were reported
ALX-0061 – global licensing deal with AbbVie

**Economics**
- $175M upfront at signing in September 2013
- $665M total potential milestones plus double-digit royalties

**Ablynx**
- perform and fund Phase I study with subcutaneous formulation (started 2014)
- perform and fund Phase II studies in RA and SLE (start 2015)

**AbbVie**
- pay a fee for each indication if they exercise the right to license ALX-0061 after completion of the Phase II studies
- responsible for Phase III development and registration

**Commercialisation**
- AbbVie is responsible for global commercialisation
- Ablynx retains option to co-promote ALX-0061 in the Benelux

RA: rheumatoid arthritis    SLE: systemic lupus erythematosus
ALX-0061 – key data points in clinical development

Phase I sc study
- results announced 23 Oct 2014
  ALX-0061 showed >80% bioavailability after sc injection

Phase II in RA
- top line results
  potentially continues development in RA

Phase II in SLE
- top line results
  potentially continues development in SLE
Additional clinical assets

- **ALX-0761** – anti-IL-17A/F licensed to Merck Serono
- **ALX-0141** – anti-RANKL licensed to Eddingpharma (rights in Greater China)
- **Ozoralizumab** – anti-TNFα licensed to Eddingpharm (rights in Greater China)
ALX-0761 – bi-specific Nanobody in psoriasis

ALX-0761 blocks both IL-17A and IL-17F (involved in inflammation); binds human serum albumin for improved PK

Targeting both IL-17A and IL-17F could be more effective in blocking the inflammatory response
  - IL-17F forms homodimer and heterodimers with IL-17A
  - IL-17F exerts similar in vitro biological activity as IL-17A but is secreted by different cell types

Development by Merck Serono
  - completed Phase I SAD study in healthy volunteers
  - ongoing Phase Ib study in patients with psoriasis (results expected in 2016)

Secukinumab (Novartis) most advanced anti-IL-17A in development (registration phase) with estimated peak sales of ~$500M*

*Analysts estimates 2014

1Poster available on Ablynx website: R&D-pipeline
Clinical stage products licensed in China

Total pharma market in China expected to grow to $163bn by 2017

Anti-TNFα – ozoralizumab – inflammation

- Phase II proof-of-concept achieved in patients with RA (Pfizer)
- Ablynx regained worldwide rights to anti-TNFα Nanobodies from Pfizer
- exclusively licensed to Eddingpharm in Greater China in Aug 2014
  - €2M upfront; development and commercial milestones; up to 20% royalties
- pre-clinical study in China on-going
- Ablynx will have access to the clinical data generated by Eddingpharm

Anti-RANKL – ALX-0141 – bone disorders

- Phase I study successfully completed (Ablynx)
- exclusively licensed to Eddingpharm in Greater China in Oct 2013
  - €2M upfront; commercial milestones; up to 20% royalties
- pre-clinical study in China currently on-going
- Ablynx will have access to the clinical data generated by Eddingpharm

\(^1\) Espicom
Partnerships

Nanobodies® - Inspired by nature
Broad platform exploitation and cash generation

Global licensing deal for ALX-0061 (anti-IL-6R) in RA and SLE: $175M upfront and total potential value of $840M plus royalties

Strategic discovery alliance (8 pre-clinical programmes on-going) – focus on bi-specifics

4 deals: 10 programmes (1 Phase I) on-going in inflammation, immunology, oncology, immune-oncology, neurology and osteoarthritis

2 discovery deals: ion channel deal in neurology; immune-onco deal (focus on multi-specifics) with €20M upfront, €10.7M research funding and total potential milestones of up to €1.7bn plus royalties

2 licensing deals in Greater China for ALX-0141 (anti-RANKL) in bone disorders and ozoralizumab (anti-TNFα) in inflammation

Target based discovery deal (challenging target: CXCR2)

>€335M in non-dilutive cash received from collaborators to date

~€3Bn in potential future milestones plus royalties
Nanobodies® - Inspired by nature

Outlook
A successful 2014 and a strong 2015 ahead

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<th>2014 achievements</th>
<th>Potential value enhancing events in 2015</th>
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<tr>
<td>• 5 clinical trial read outs including clinical proof-of-concept (POC) for caplacizumab in TTP - data being presented at ASH</td>
<td>• Start of Phase IIb with ALX-0061 (IL-6R) in RA</td>
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<tr>
<td>• 4 clinical trials initiated</td>
<td>• Start of Phase III with caplacizumab (vWF) in TTP</td>
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<tr>
<td>• Further validation of the platform through immune-onco deal with Merck &amp; Co focusing on multi-specifics</td>
<td>• Start of Phase IIA with ALX-0061 (IL-6R) in SLE</td>
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<tr>
<td>• Expansion into Asia through 2nd licensing deal with Eddingpharm for the development and commercialisation of ozoralizumab in Greater China</td>
<td>• Start of multiple Phase I studies for partnered programmes</td>
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<td>• Results from various technology feasibility studies across multiple applications</td>
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<td>• Results from Phase IIA with ALX-0171 (RSV) in infants, potentially the 4th clinical POC for Ablynx</td>
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<td>• Continued discussions on partnering various early stage and later stage assets</td>
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<td>• Milestone payments from on-going partnerships</td>
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Value creation – clinical data expected from patient studies

2014
- caplacizumab Phase II (TTP)
  - Wholly-owned

2015
- ALX-0171 Infant Phase IIa (RSV)
  - Wholly-owned
- ALX-0761 Phase Ib (severe psoriasis)
  - Licensed to Merck Serono (worldwide)
- AbbVie have option to license worldwide

2016
- ALX-0061 Phase IIb (RA)
  - AbbVie have option to license worldwide
- ALX-0171 Infant Phase IIb (RSV)
  - Wholly-owned
- ALX-0141 and ozoralizumab Phase I/II in China
  - Licensed to Eddingpharm (China)

2017
- caplacizumab Phase III (TTP)
  - Wholly-owned
- ALX-0061 Phase IIa (SLE)
  - AbbVie have option to license worldwide

2018
- Results from a number of patient studies with partners
- ALX-0061 Phase IIa (SLE)
  - AbbVie have option to license worldwide
Nanobodies® – creating better medicines

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