Ablynx

Nanobodies®
Innovative therapeutics

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

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

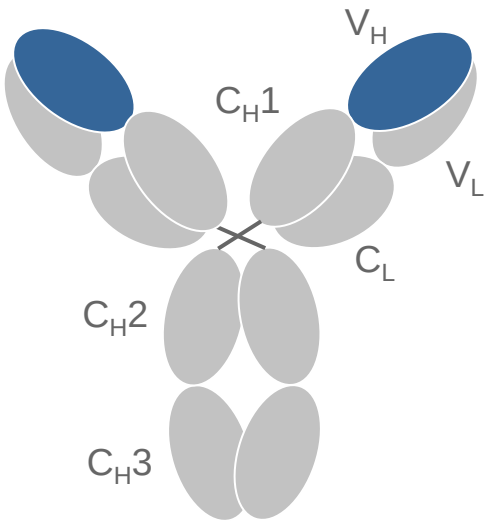
FINANCIALS

- €206M in cash at December 31st 2014

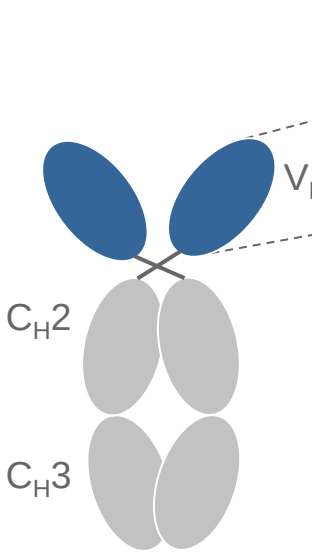
Nanobodies

Derived from heavy-chain only antibodies

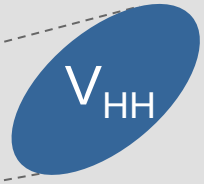
- *Camelid* heavy-chain only antibodies are stable and fully functional
- Nanobodies represent the next generation of antibody-derived biologics



Conventional antibodies



Heavy chain only antibodies



12-15kDa

Ablynx's Nanobody

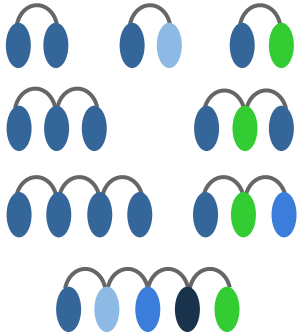
- small
- robust
- sequence homology comparable to humanised/human mAbs
- easily linked together
- nano- to picomolar affinities
- intractable targets
- multiple administration routes
- manufacturing in microbial cells

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

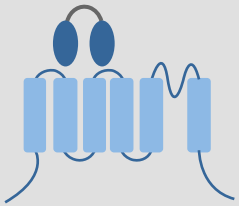
Nanobody platform

Competitive advantages

Mix and match

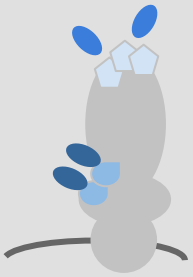
Targeting different pathways at once with a single Nanobody construct, e.g. multiple checkpoint inhibitors

Challenging and intractable targets



Nanobodies against ion channels and GPCRs

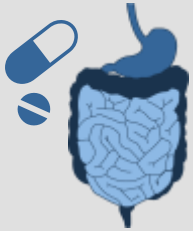
Nanobodies can reach conserved cryptic epitopes



Alternative delivery routes

Inhalation

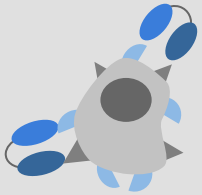
Needle-free



Oral-to-topical

Ocular

Cell- /tissue-homing



Cell specificity

Immune cell recruitment

Tissue-specific targeting

Customised half-life extension

Weeks/days/hours

Fc

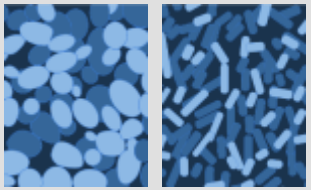
Albumin-binding Nanobody

Cell killing

Nanobody-drug conjugates

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® used as prophylaxis in high-risk and/or pre-term infants only




Evolves to distressing symptoms → **Symptomatic treatment including e.g. inhaled bronchodilator** → **8-20% hospitalised**

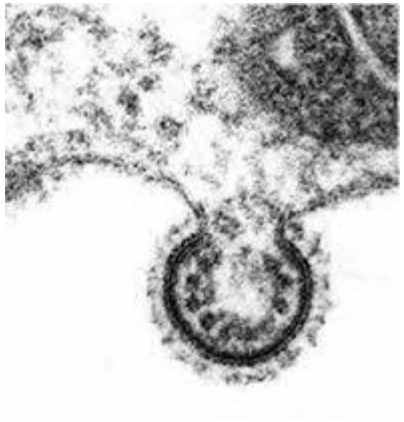
* Extrapolation based on estimated US prevalence

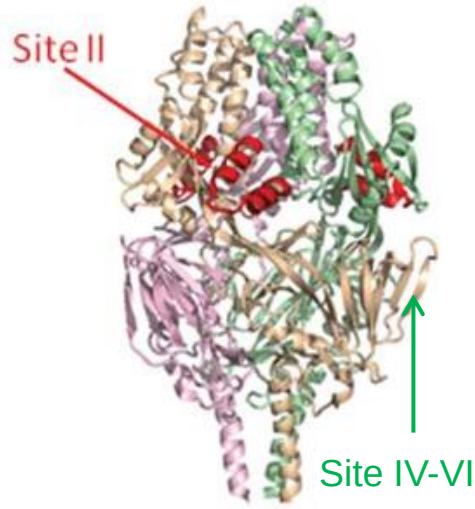
[1] Hall et al, NEJM, 2009; [2] Lee et al, Human Vaccines, 2005; [3] Shi et al, J Med Econ, 2011; [4] Sigurs et al, Thorax, 2010; Backman et al, Acta Pediatr, 2014

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





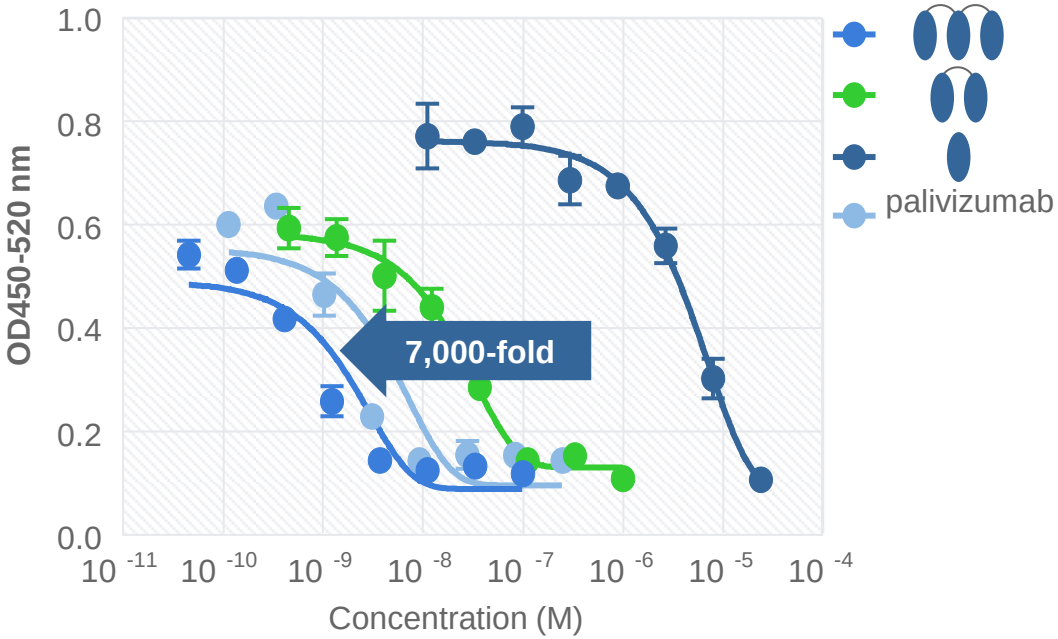
RSV F-protein
(pre-fusion)

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

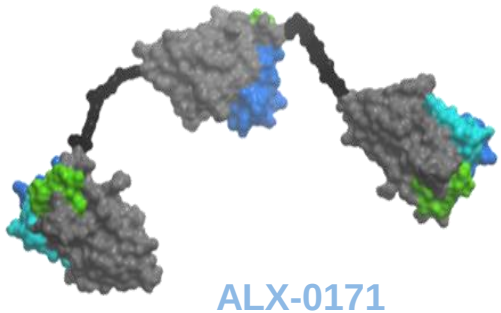
Increased potent strain coverage

- 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)

	A-strain	B-strain	Total
n	32	29	61
palivizumab	0 (0%)	11 (38%)	11 (18%)
ALX-0171	30 (94%)	23 (79%)	53 (87%)
p value	<0.0001	<0.0001	<0.0001

Number of strains neutralised below LLOD

Increased neutralisation capacity against a broad panel of RSV isolates



ALX-0171

anti-RSV Nanobody

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

Parameter	ALX-0171 Release Specification [a]	ALX-0171 post-nebulisation [b]
Appearance	Free of visible particles	Free of visible particles
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)

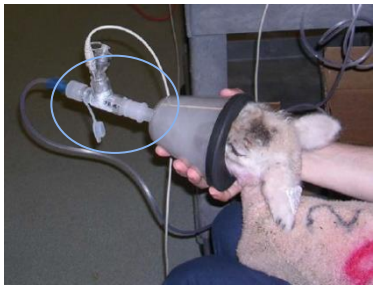
[a] For clinical Phase I/II material.
[b] Results after nebulisation of ALX-0171 GMP Drug Product upon 36 months storage at long-term storage conditions (5°C ± 3°C).
[c] NGI measurement performed at release.

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

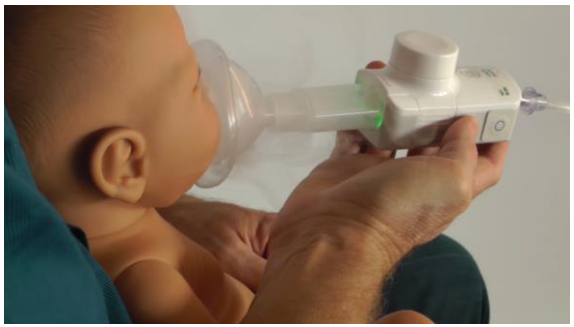
Customised infant inhalation device

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



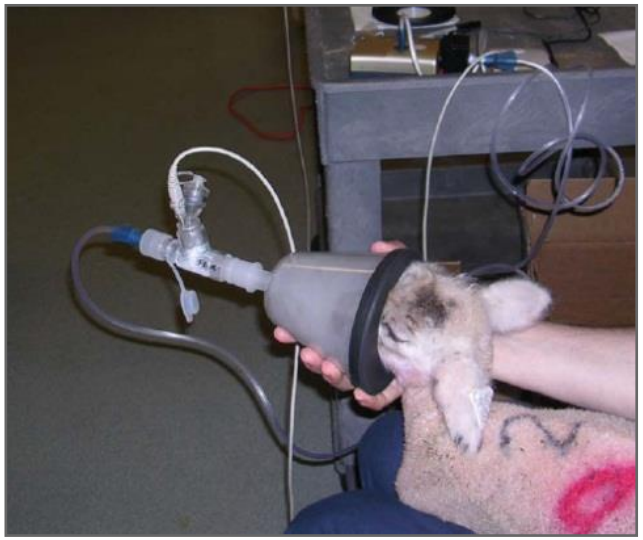
- Phase 1: three studies in adults
  - Akita^2 Apixneb (oral inhalation, breath-actuated)
  - vibrating mesh: ≈4 µm particles
  - established large safety window: maximal lung deposition

- 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 O_2 supply during treatment

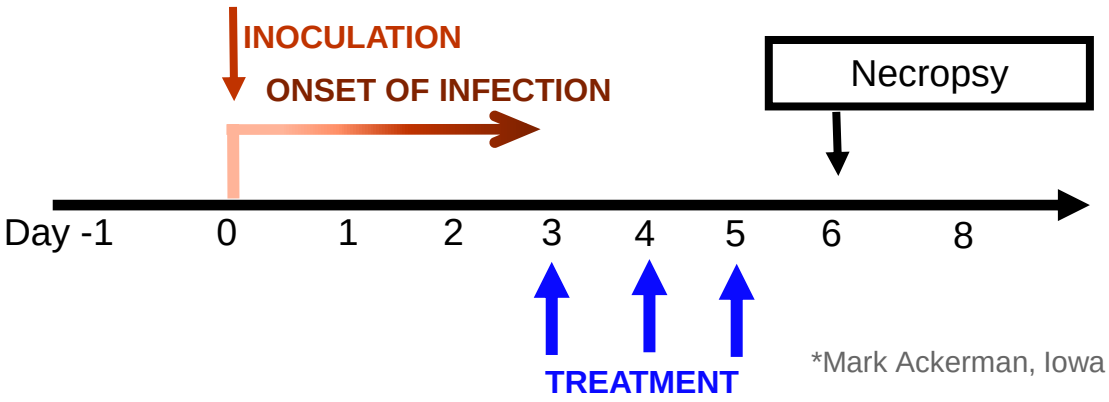


Neonatal lamb model*

In vivo study design



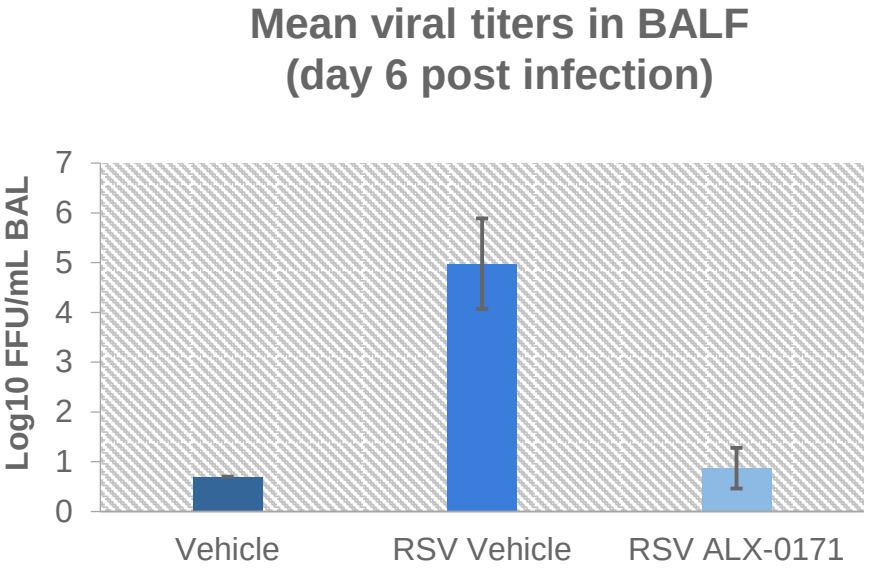
- Lambs develop lower respiratory tract infection which is associated with general malaise and specific lung pathology (comparable to infants)
- Treatment at peak of viral load on day 3 post infection (symptoms and lung pathology are already clearly present)
- Lambs develop clinical symptoms such as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

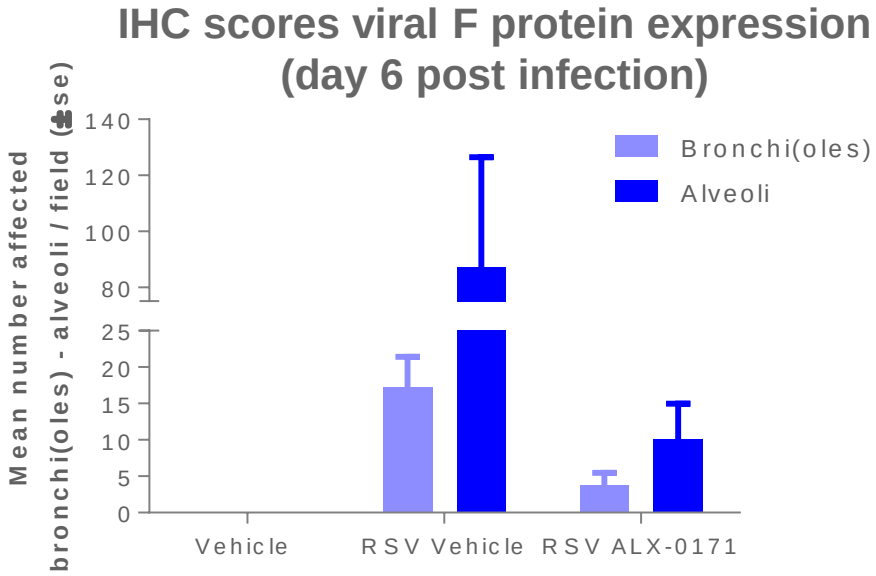


*Mark Ackerman, Iowa State University

ALX-0171 *in vivo* study

*P*roof-of-concept achieved in neonatal lambs





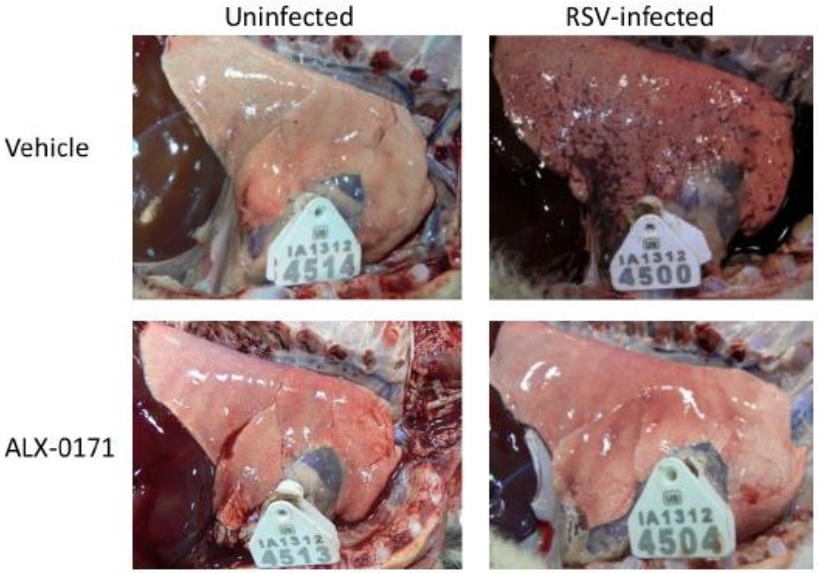
ALX-0171 treatment results in

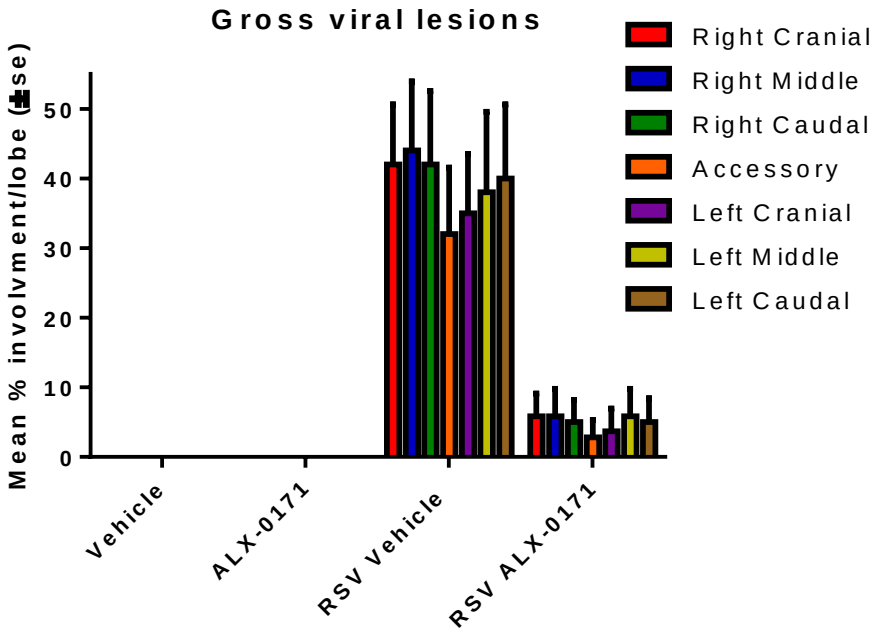
- strong reduction of viral titres in bronchoalveolar lavage fluid (BAL)
  - coincides with strong reduction F protein expression
- strong reduction of gross viral lung lesions (% involved lung tissue)
- a clear effect on general health status
  - weakness, depression, lethargy, drooping of ears, not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

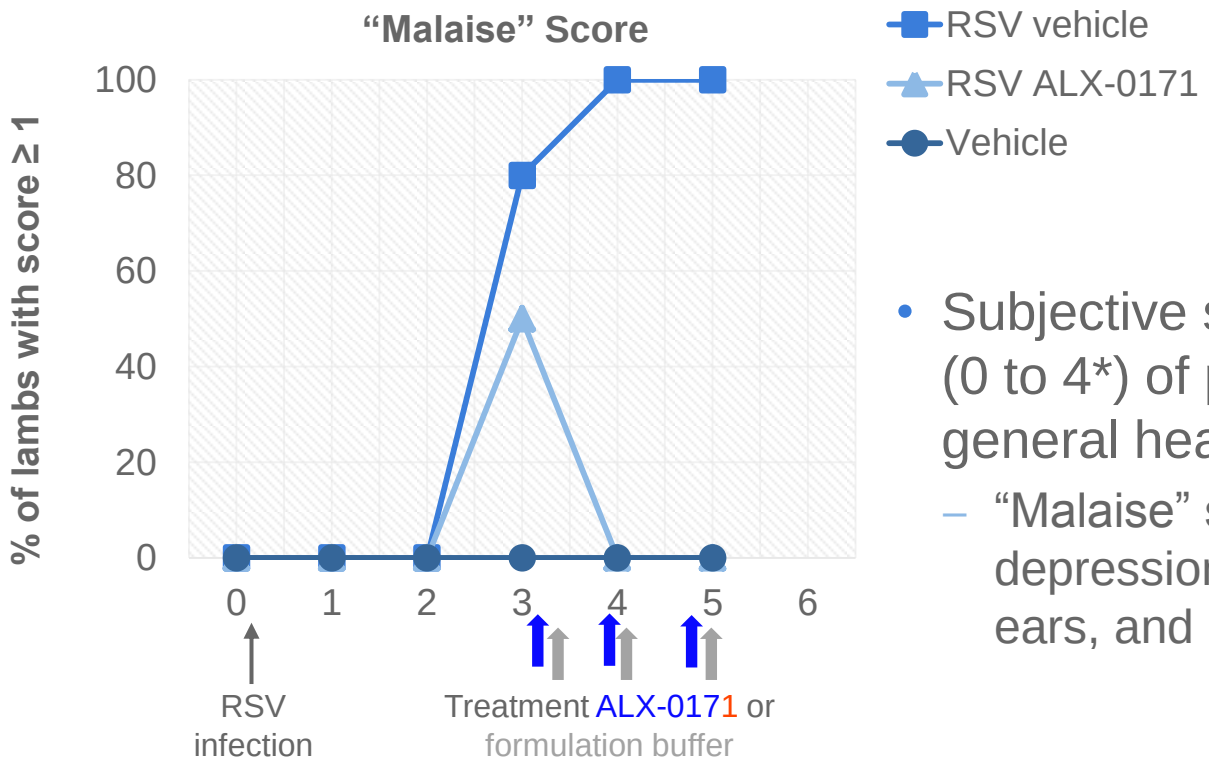




Daily inhalation of ALX-0171 markedly reduced gross lung viral lesions

ALX-0171 *in vivo* study

Strong effect on general health status of RSV-infected lambs



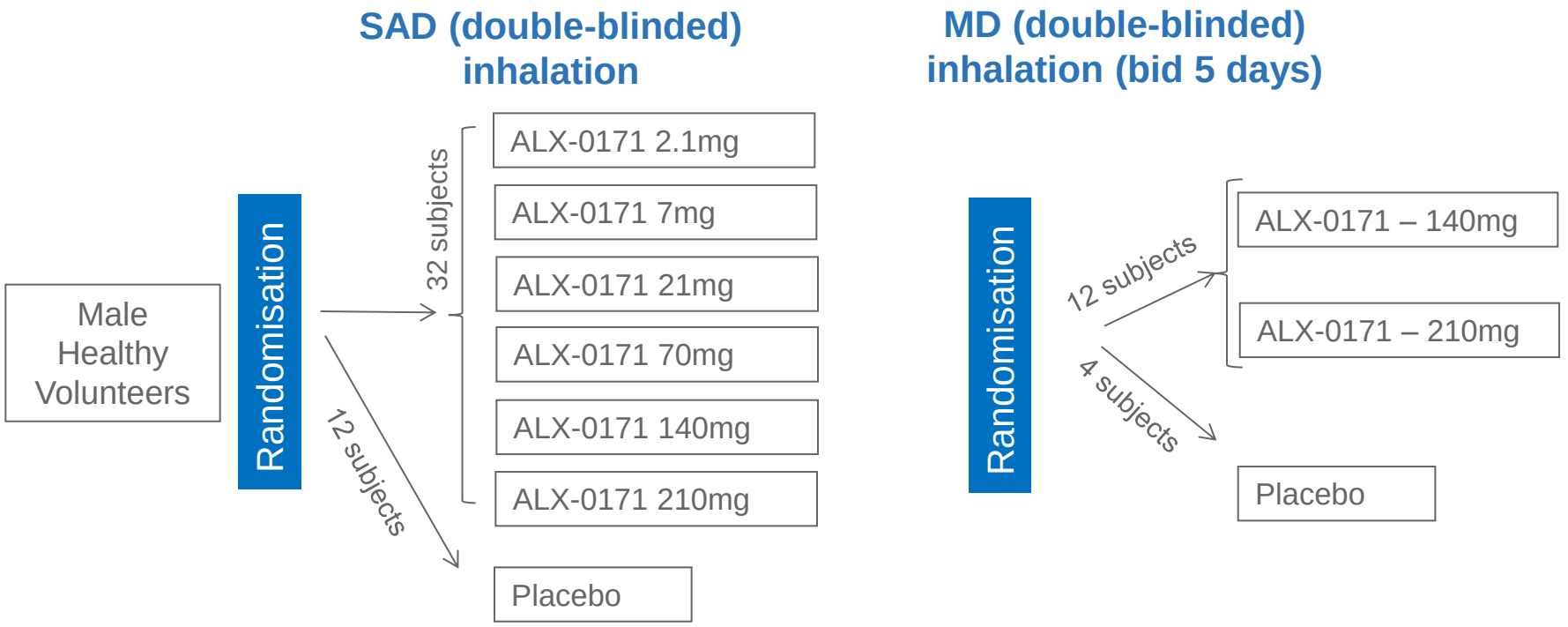
- Subjective scoring (0 to 4*) of parameters that measure general health
  - "Malaise" score: weakness, depression, lethargy, drooping of ears, and not eating

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 occured
  - 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

Acknowledgements

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IWT, Belgium

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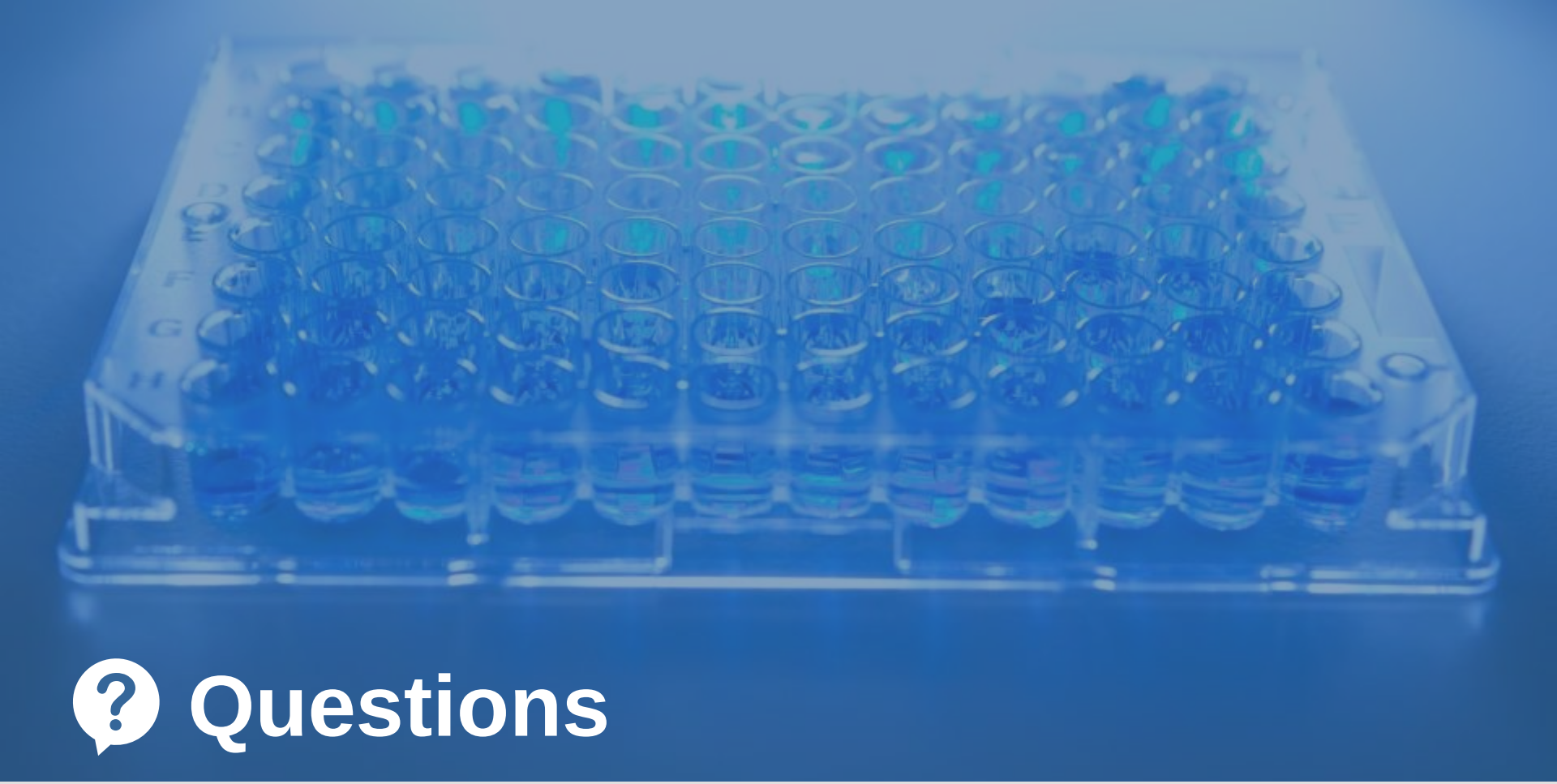

Questions

CONTACT DETAILS

Investor Relations

+32 9 262 00 00

investors@ablynx.com

www.ablynx.com

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