



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

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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)
- 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

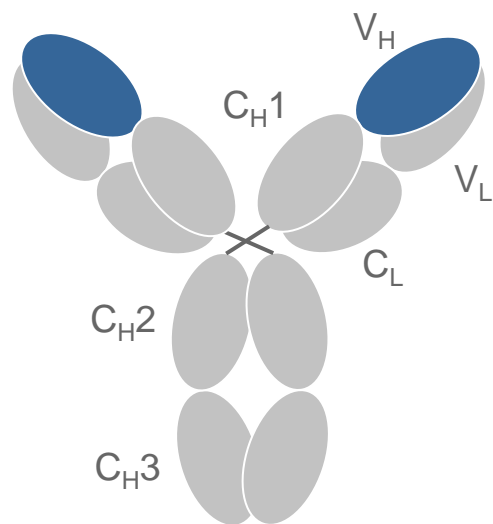
FINANCIALS

- €206M in cash at December 31st 2014

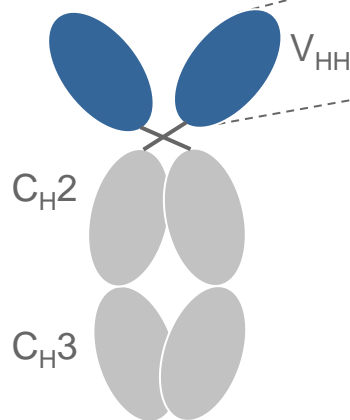
Nanobodies

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

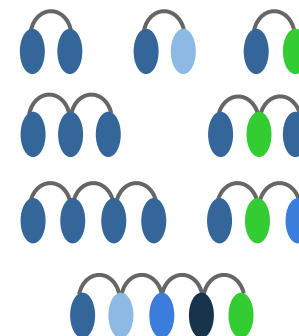
Rapid generation of high quality biologics



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

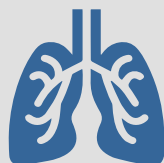
Competitive advantages

Mix and match

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



Alternative delivery routes



Inhalation



Needle-free



Oral-to-topical



Ocular

Customised half-life extension



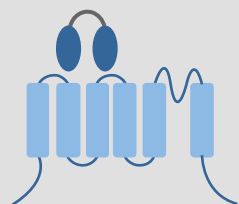
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Weeks/days/hours



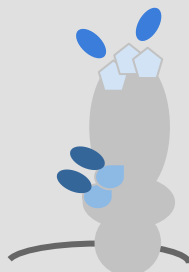
Albumin-binding Nanobody

Challenging and intractable targets



Nanobodies against ion channels and GPCRs

Nanobodies can reach conserved cryptic epitopes

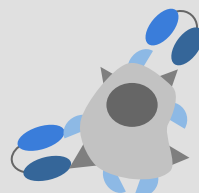


Cell killing

Nanobody-drug conjugates



Cell- /tissue-homing



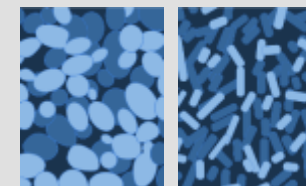
Cell specificity

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 infection³
 - prolonged wheezing and increased risk for asthma development⁴
- 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**

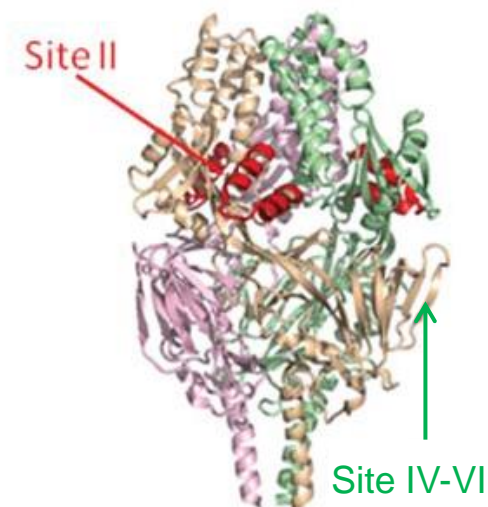
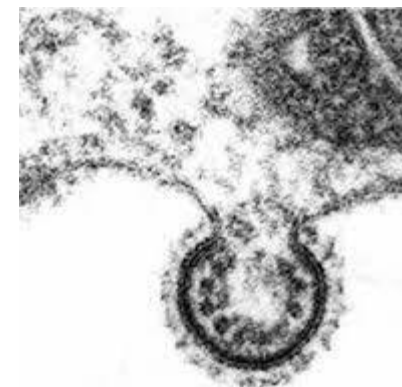
* Extrapolation based on estimated US prevalence

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 Paediatr, 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



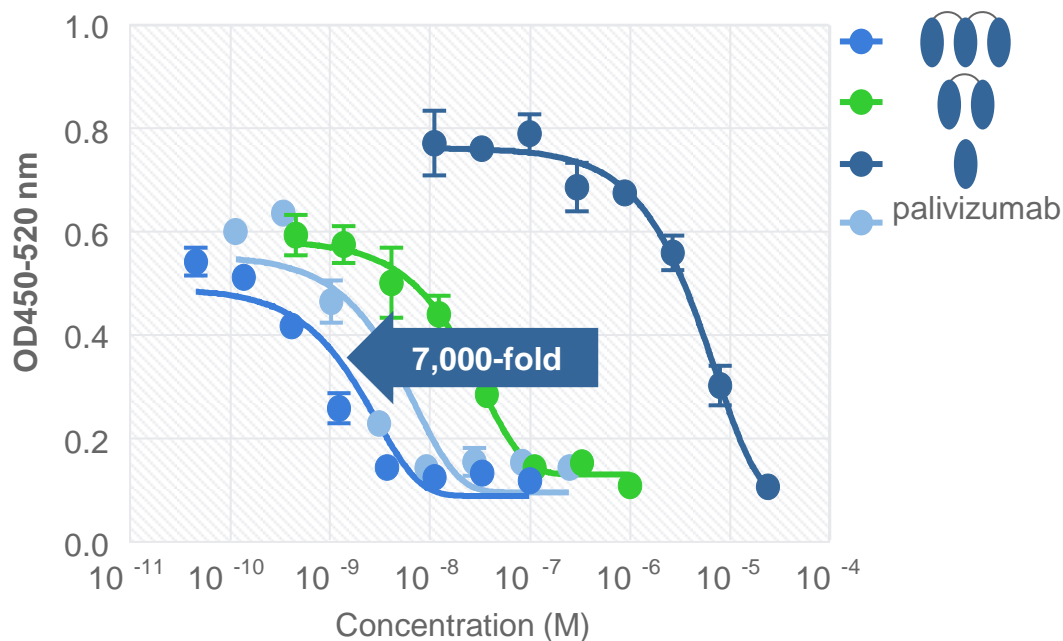
RSV F-protein
(pre-fusion)

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

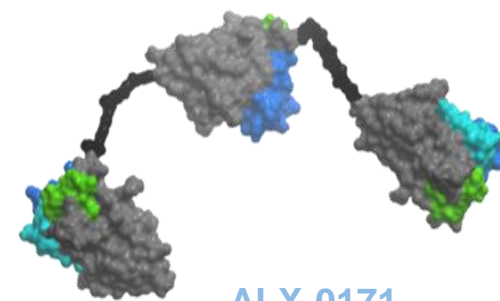
Increased potent strain coverage

- 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	<ul style="list-style-type: none"> • OD280: 50 ± 10 mg/ml • Absorbance at 340 nm 	<ul style="list-style-type: none"> • 46.7 mg/ml • 0.000
SE-HPLC	<ul style="list-style-type: none"> • ≥ 85% main peak • ≤ 5% HMW 	<ul style="list-style-type: none"> • ≥ 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.

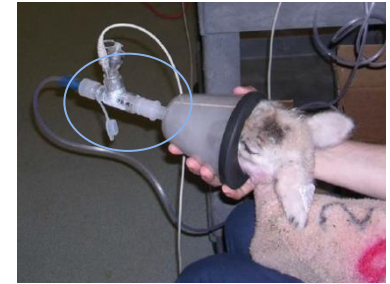
^b Results after nebulisation of ALX-0171 GMP Drug Product upon 36 months storage at long-term storage conditions (5°C ± 3°C).

^c NGI measurement performed at release.

Device development throughout the project

Customised infant inhalation device

- Lamb studies
 - vibrating mesh: $\approx 3 \mu\text{m}$ particles for smaller airways
 - nasal inhalation (cone)
- Phase 1: three studies in adults
 - Akita² Apixneb (oral inhalation, breath-actuated)
 - vibrating mesh: $\approx 4 \mu\text{m}$ 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: $\approx 3 \mu\text{m}$ particles
 - nasal inhalation (soft face mask)
 - continuous air or O₂ supply during treatment

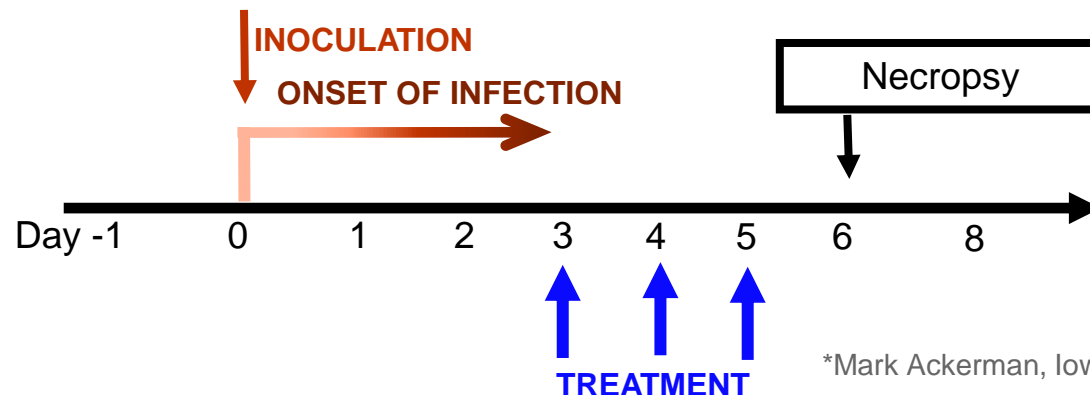


Neonatal lamb model*

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)

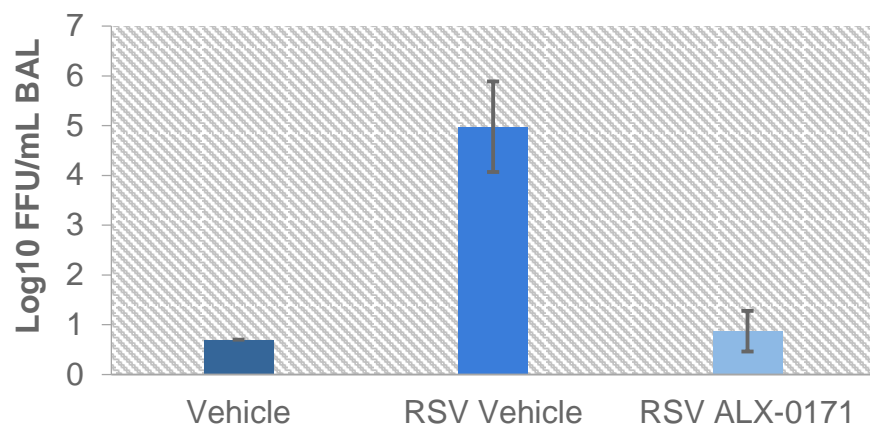


*Mark Ackerman, Iowa State University

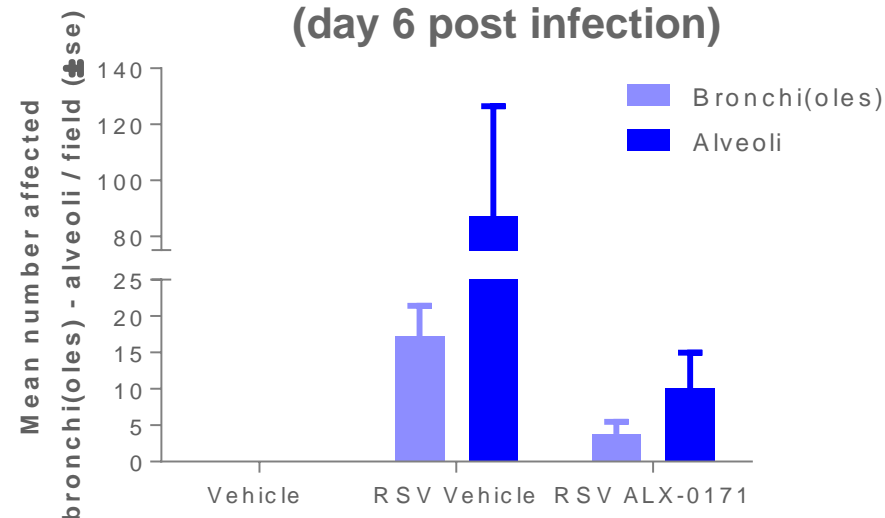
ALX-0171 *in vivo* study

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)



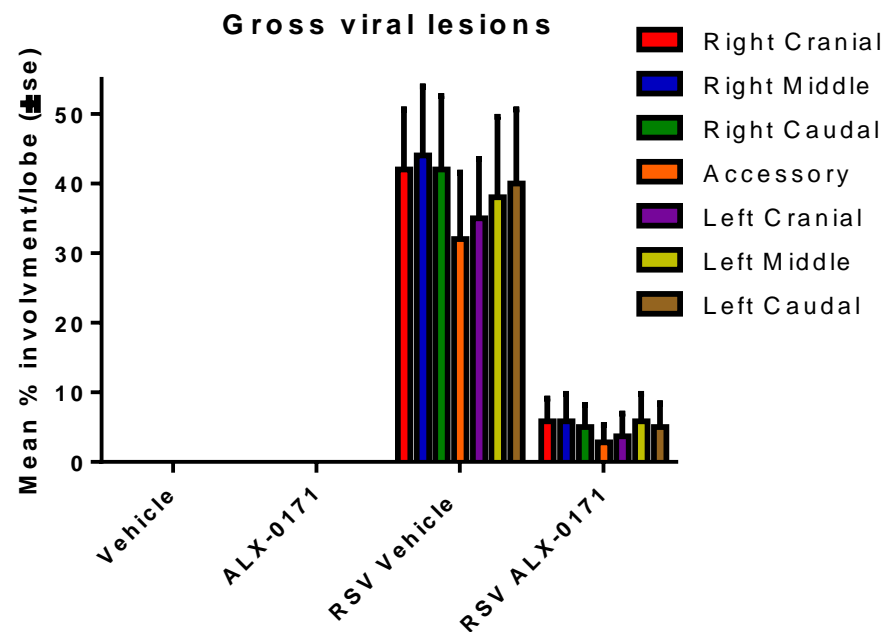
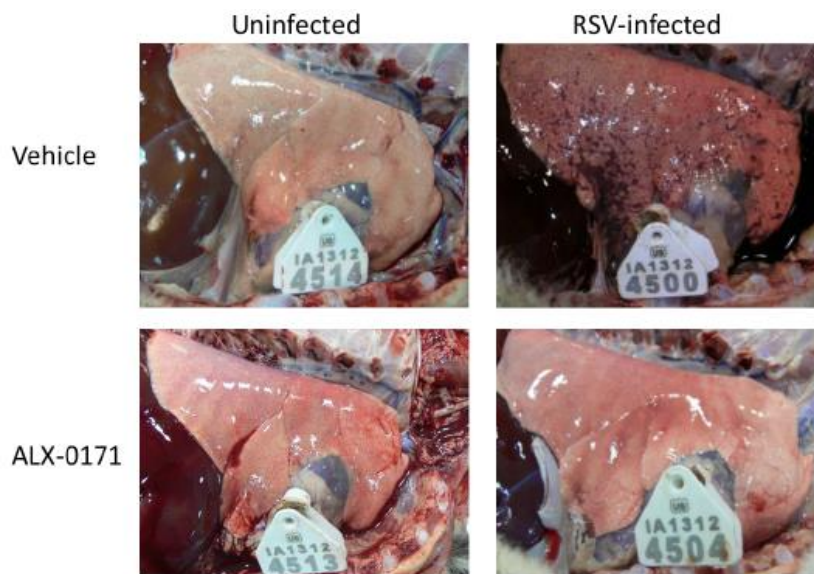
ALX-0171 treatment results in

- 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

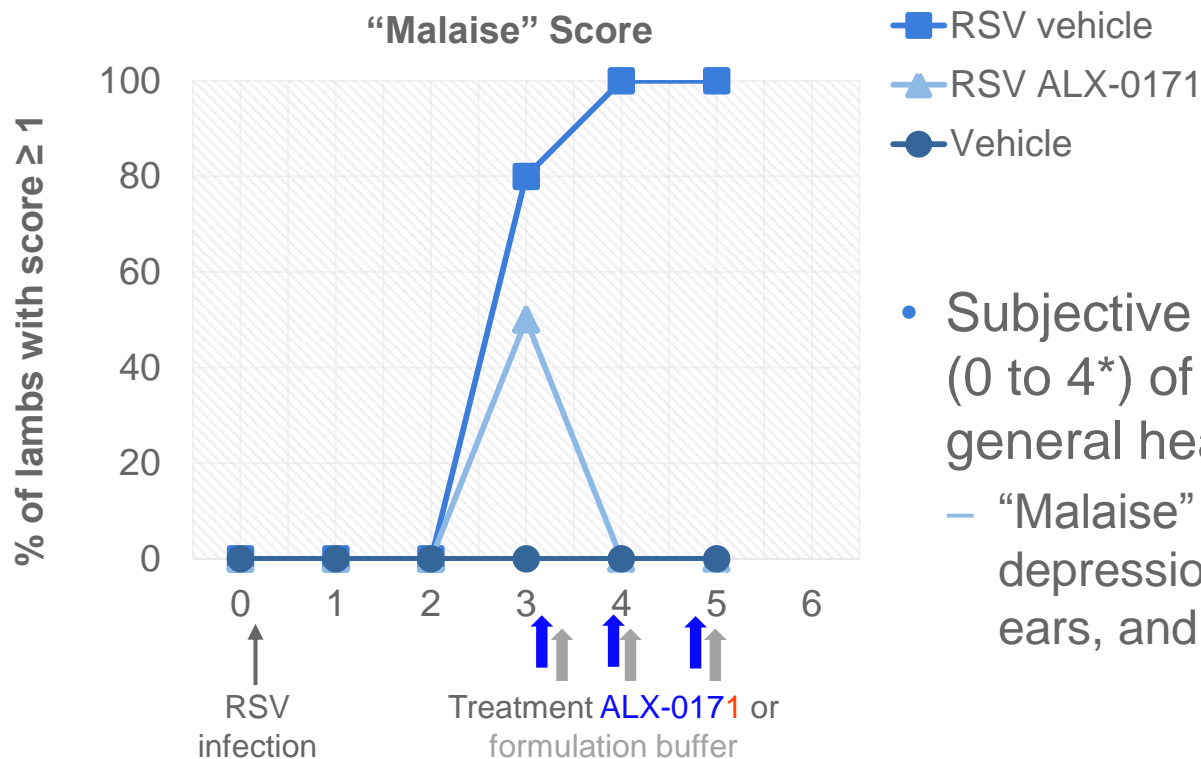
- Plum red RSV lesions seen in lungs of RSV-infected lambs on day 6 post-infection
 - present on all lung lobes assessed



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

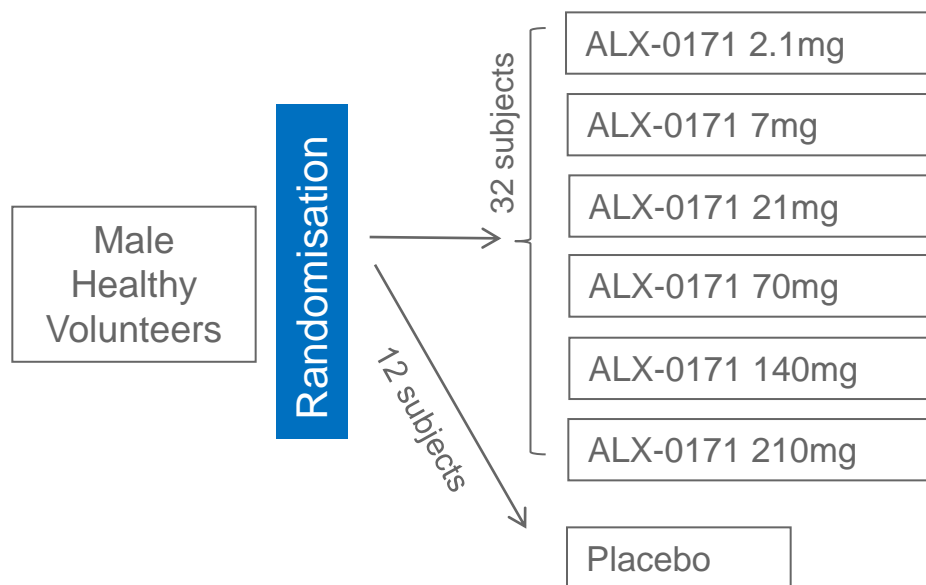
Daily inhalation of ALX-0171 markedly reduced symptoms of illness in RSV infected neonatal lambs

* 0 = no clinical signs; 4 = animals down

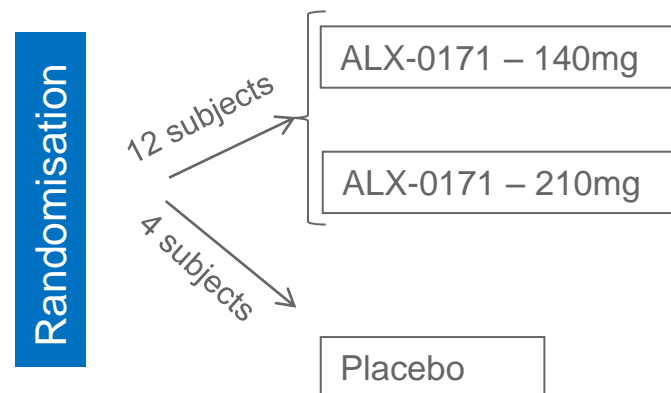
ALX-0171 – Phase I

Study design

SAD (double-blinded) inhalation



MD (double-blinded) inhalation (bid 5 days)



- 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)

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 \approx 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

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



Ablynx, Gent, Belgium

The RSV core and project team

- Koen Allosery
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- Catelijne Stortelers
- Katrien Vlassak
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Mark Ackermann and team



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Brian Gilbert, Pedro A Piedra and teams



Instituto de Salud Carlos III, Spain

José Melero and team



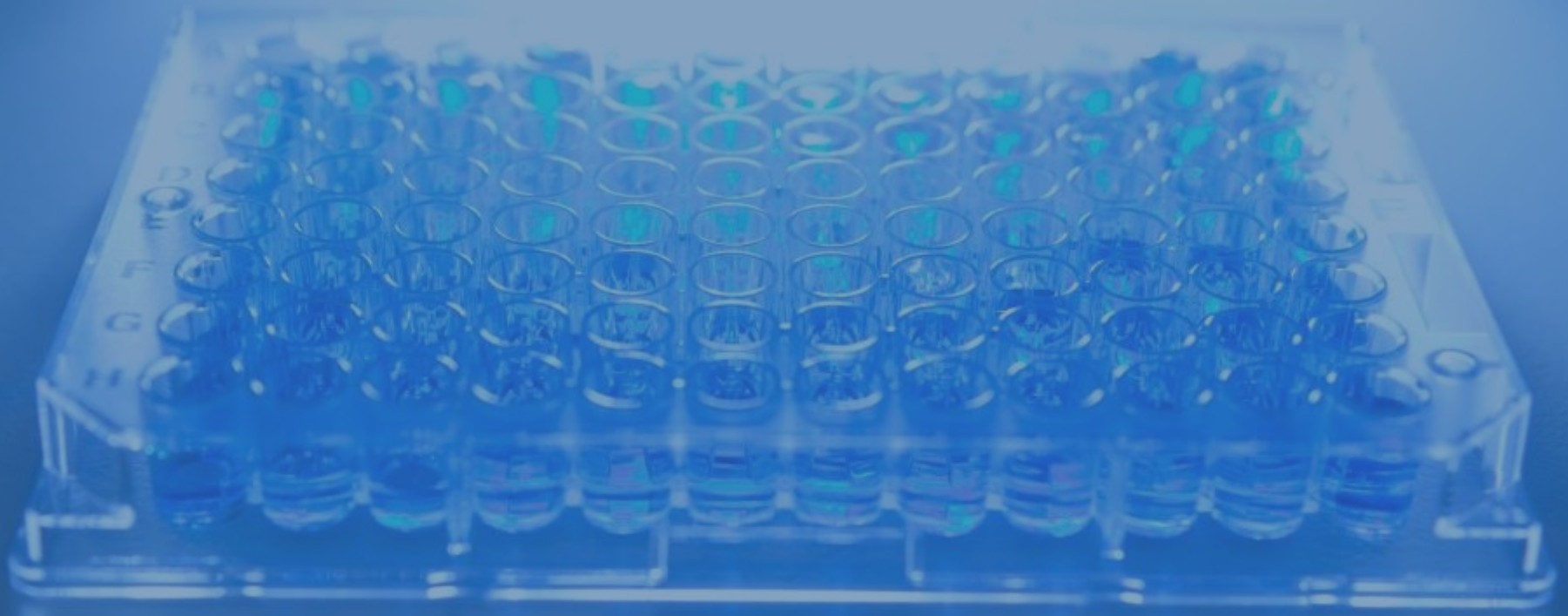
Vectura Group plc



IWT, Belgium

- Grant 100333 and 130562





Questions

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