Nanobodies®: journey from research to commercial

UPIP-VAPI

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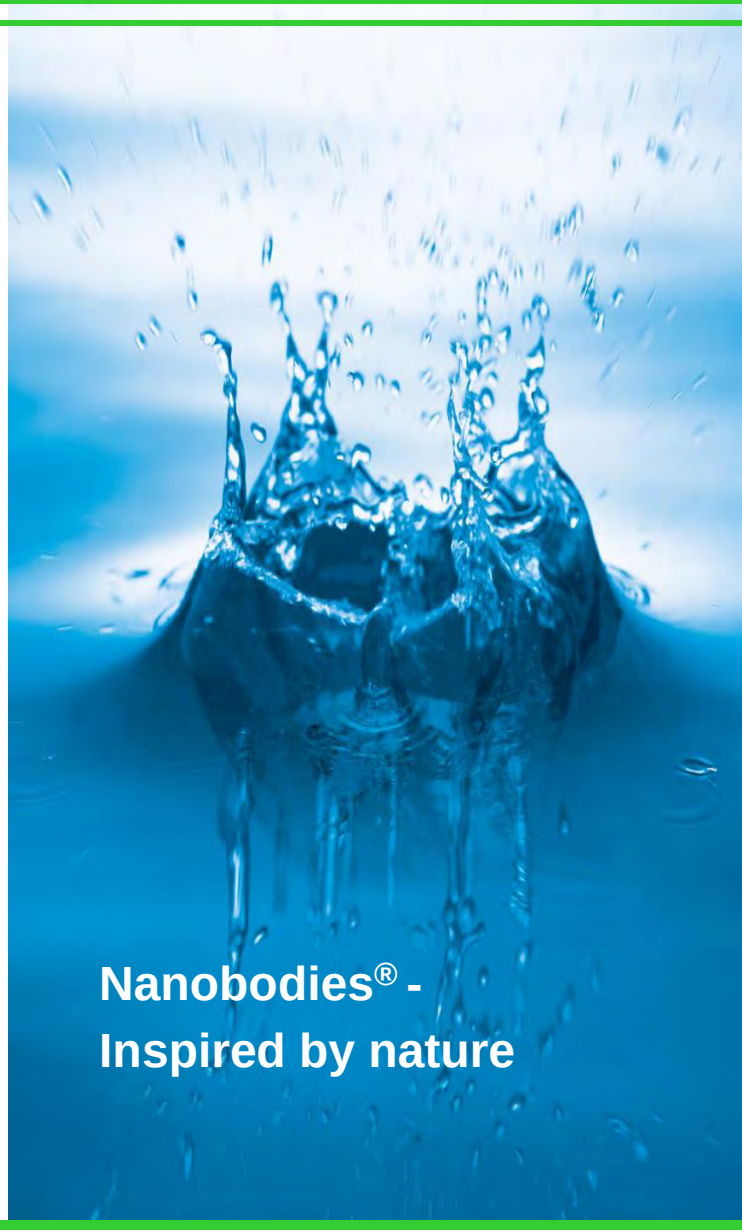

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Outline

- From research to commercialization
  - The story of Ablynx
- The Nanobody technology
- Product pipeline and examples of clinical assets
  - anti-IL-6R to treat RA – strong efficacy and safety results in Phase II
  - anti-vWF (caplacizumab) to treat TTP
  - anti-RSV

Creating a Spin-Off Company: steps and issues involved

Commercialization via Start-up/Spin-Off Company

- What do you need to create a Start-up/Spin-Off Company?

- An invention arises from university research
- A platform technology is built up
- If the technology (invention) is a platform on which could be built multiple commercial products, it can form basis for a new company
  - New business allows a researcher to be personally involved in the translation of its discoveries into products & services and see the correlation between hard work and financial reward

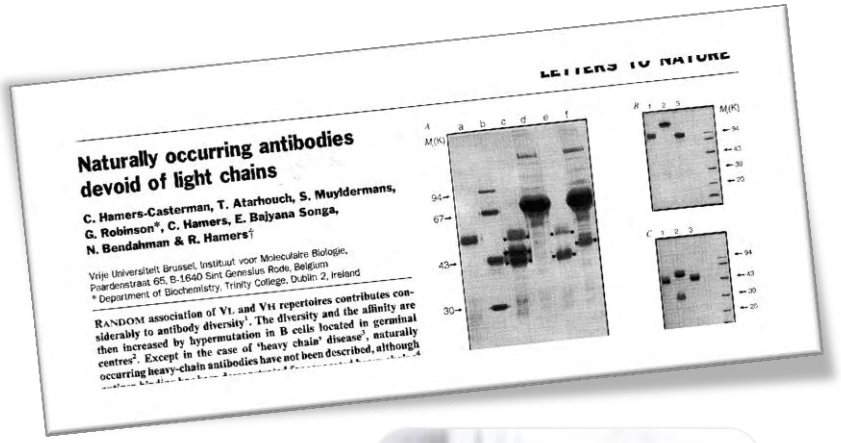
Creating a Spin-Off Company: steps and issues involved

- The Business Opportunity Document
  - A key marketing document that describes the business opportunity
- Development of Business Plan
- **Protection and exploitation of Intellectual Property**
  - Multi-layered approach (platform, drugs, formulation,…)
  - Life cycle management

- Finding investors
- Finding infrastructure
- Negotiation and legal support
- Management of growth

In the beginning….

- Early ’90: discovery of camelid heavy-chain only antibodies at ALBI (VUB)
- Further characterization and development of the V_HH platform technology
- In 1996: ALBI joins VIB
- Intensive collaboration between VIB headquarters and ALBI (VIB6) to validate the technology for potential spin-off
- Generation of IP
- Development of Business Plan
- Patent Portfolio (University/VIB)
- In 2001: ABLYNX established
- In 2002: ABLYNX incorporated (completed first financing round)
- Nanobody technology



LETTERS TO NATURE

Naturally occurring antibodies devoid of light chains

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* Department of Biochemistry, Trinity College, Dublin 2, Ireland

RANDOM association of VL and VH repertoires contributes considerably to antibody diversity[1]. The diversity and the affinity are then increased by hypermutation in B cells located in germinal centres[2]. Except in the case of 'heavy chain' disease[3], naturally occurring heavy-chain antibodies have not been described, although

R. Hamers

Rapid evolution from platform to product based company

Foundation

Discovery platform

- No partners
- €5M seed financing
- No products
- 10 staff
- Platform building

Discovery and early development

- 3 partners
- €70M private equity
- €85M IPO (NYSE)
- 11 R&D projects
- 1 Nanobody in clinic
- 144 staff
- Platform upscaling

Discovery and later development

VALUE CREATION

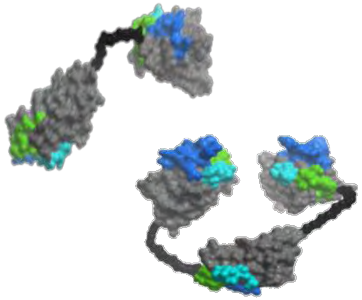
- 4 partners
- > €200M equity funding
- €160M in cash from partners
- ~ 25 R&D projects
- >700 people treated
- 7 Nanobody products in clinic
- 2 clinical POC (RA)
- < 250 staff
- Commercial production

End 2001 End 2002 End 2007 Today

Nanobodies – demonstrated track record

1st inhaled Nanobody successfully completes Phase I safety study

>750 patients and subjects have received Nanobodies



Two clinical POCs in RA

Clinical grade material produced up to 2,500L scale

Nanobodies have been tested in 18 countries, 4 continents

Three-pronged approach to balancing risk and reward

1.	Fully Funded + Milestones and Royalties	2.	Co-discovery/Co-development	3.	Wholly-owned clinical assets
	Boehringer Ingelheim, Novartis and Merck & Co •11 active programmes • €113 million in cash received since 2005 • BI is current shareholder (4.9%)		**Merck Serono – Ablynx** • 5 active programmes in inflammation, immunology and oncology • First Phase I expected in 2013 • €47 million in cash received since 2008		**Ablynx** • TNFα (ozoralizumab) – Ph II* • vWF (caplacizumab) – Ph II • IL-6R (ALX-0061) – Ph II • RANKL (ALX-0141) – Ph I • RSV (ALX-0171) – Ph I

Balancing risk and reward

€160M in non-dilutive cash from collaborators received to date

* No investment in clinical trials made to date by Ablynx

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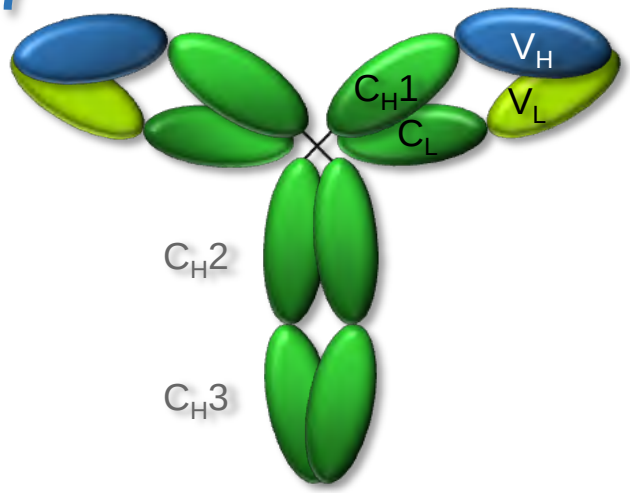
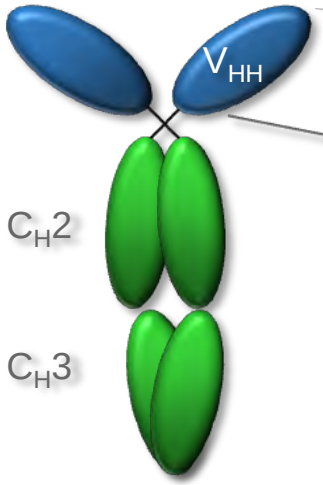
Ablynx's Nanobodies – proven single variable domain approach

Camelidae family has both forms



Conventional antibody

- Heavy and light chains
- Both chains required for antigen binding and stability
- Large size and relatively low formatting flexibility
- Administered through injection



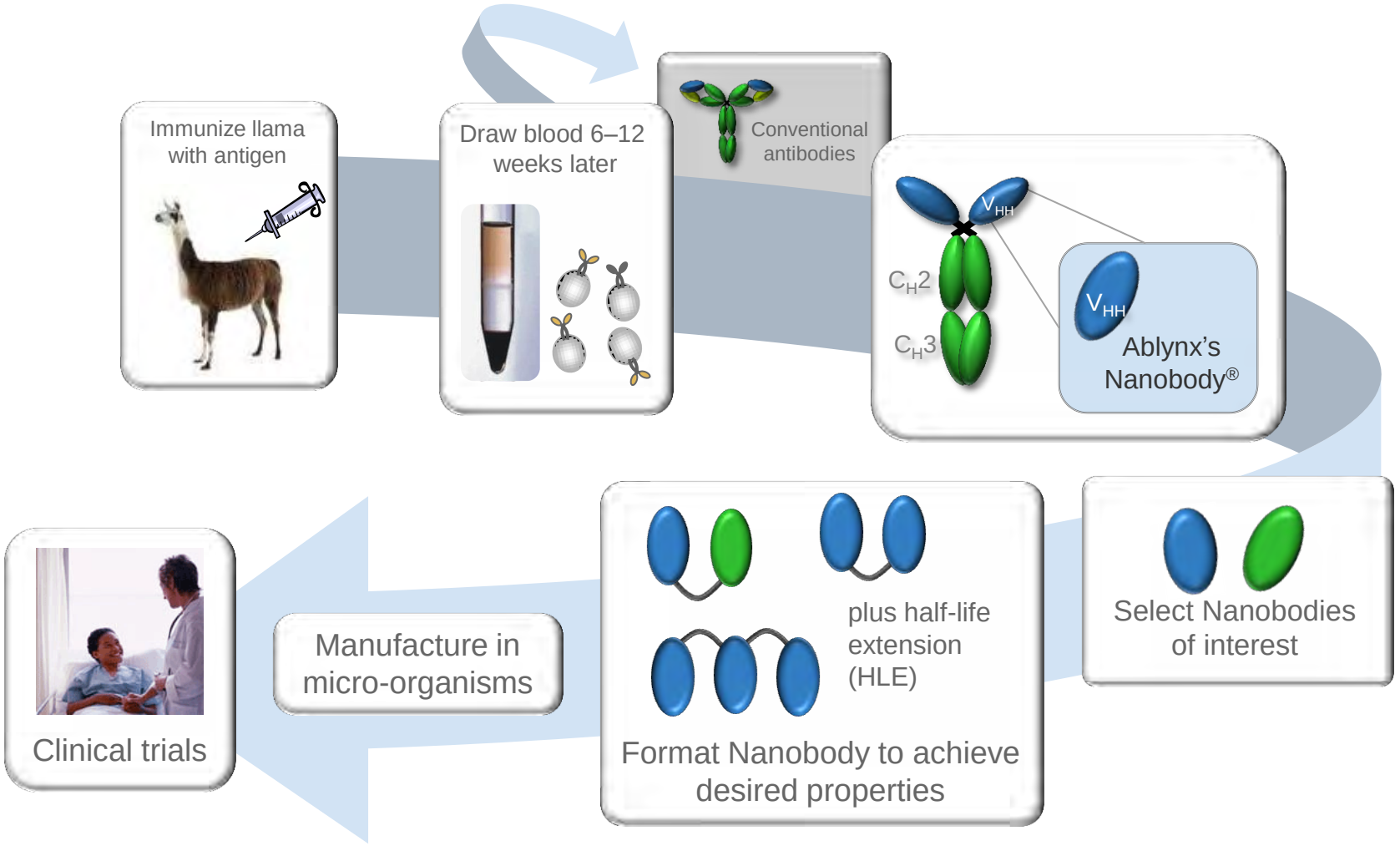
Heavy-chain antibody

- Only heavy chains
- Full antigen binding capacity and very stable

Ablynx's Nanobody®

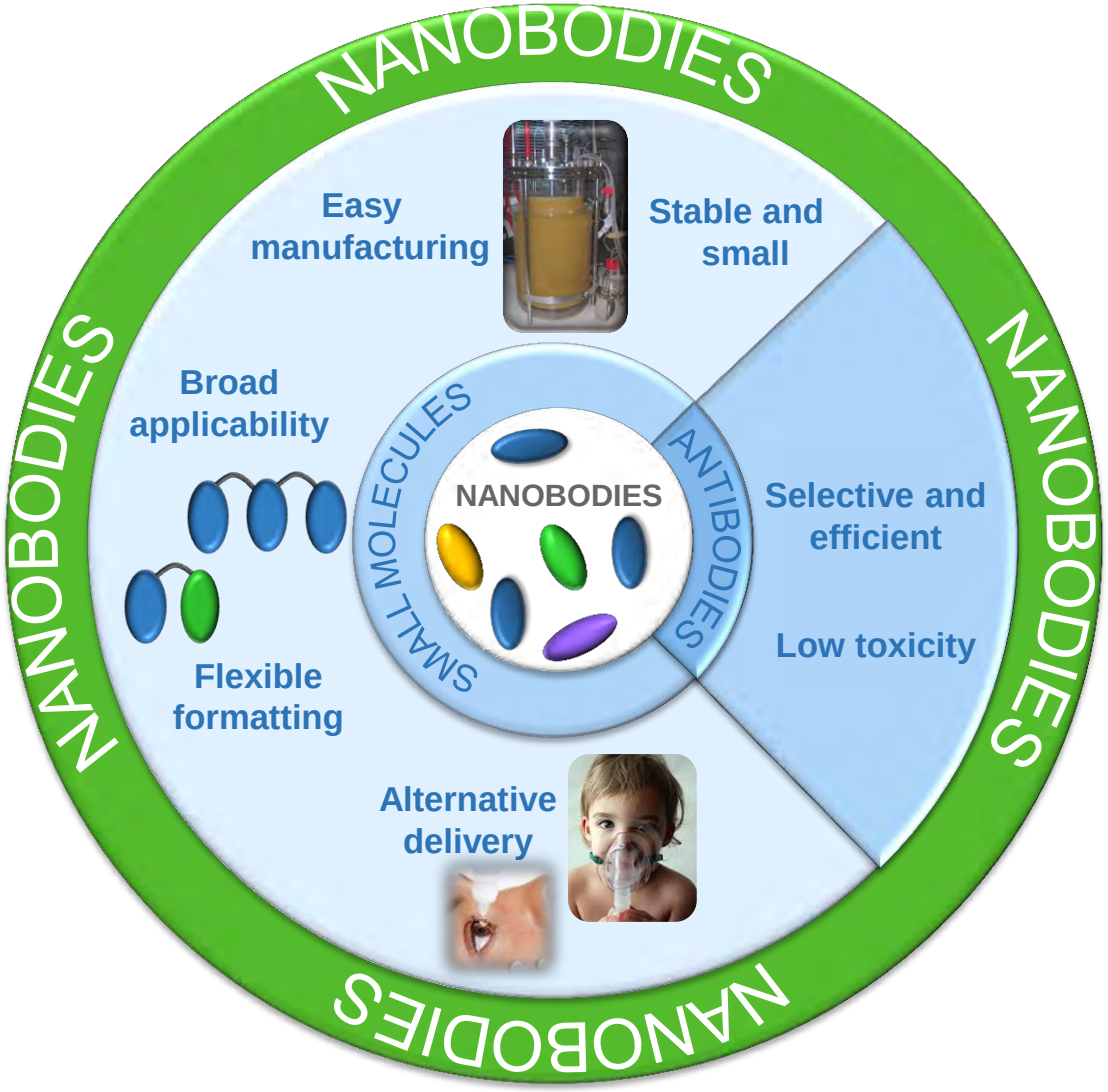
- Small (1/10 size of a mAb)
- Flexible formatting
- Highly potent, robust and stable
- Broad target applicability
- Multiple administration routes
- Ease of manufacture
- Speed of discovery

Nanobody discovery process – the power of evolution

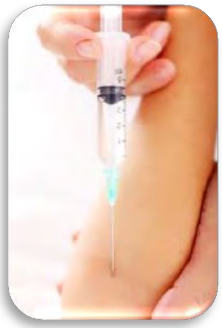


The unique potential of Nanobodies ... combines the best of both worlds

Small molecules (chemical substances)



Conventional antibodies (biological)



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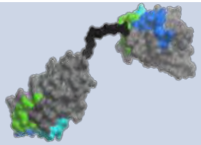
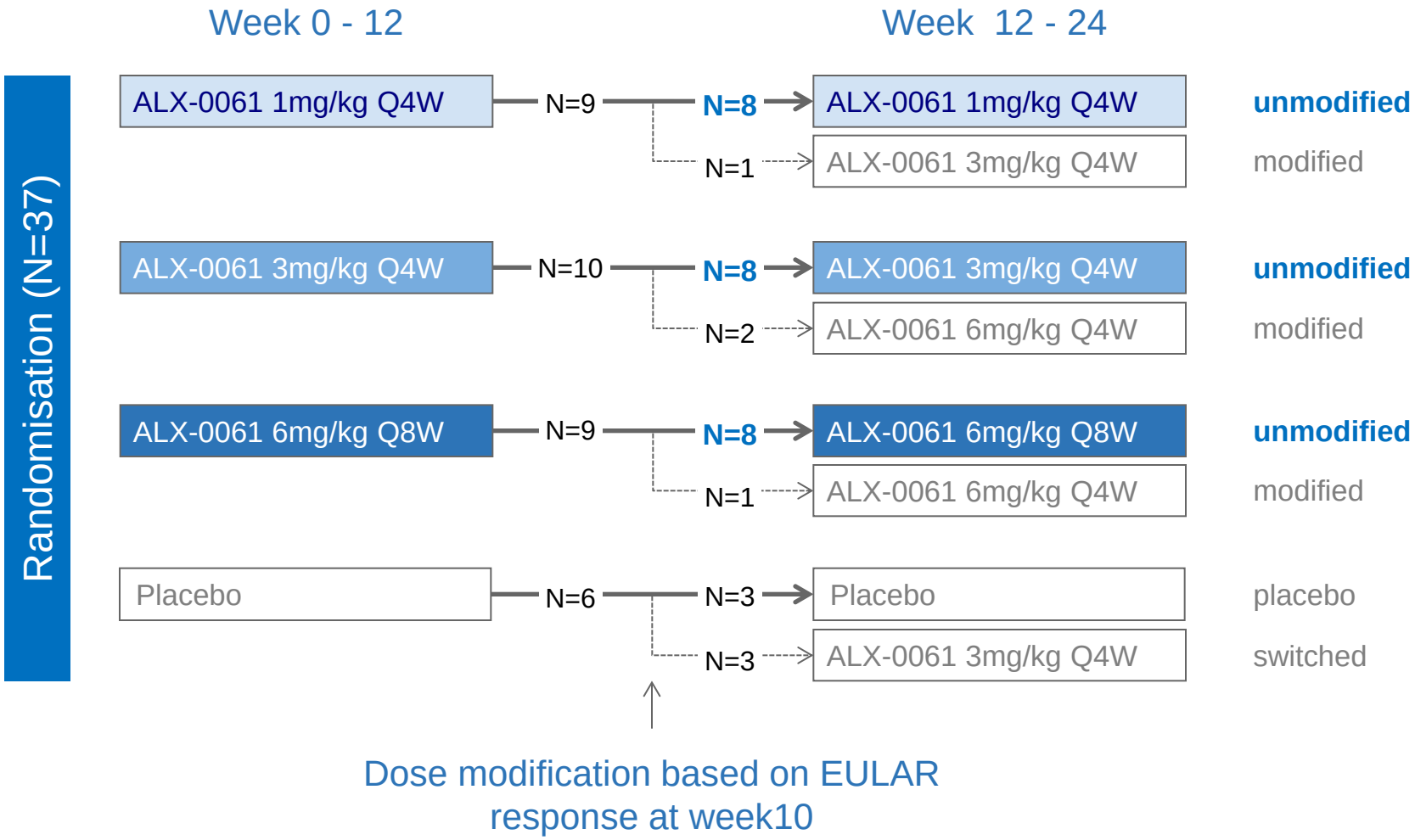
Pipeline – internal and funded programmes

ALX-0061 – designed to be potentially best-in-class

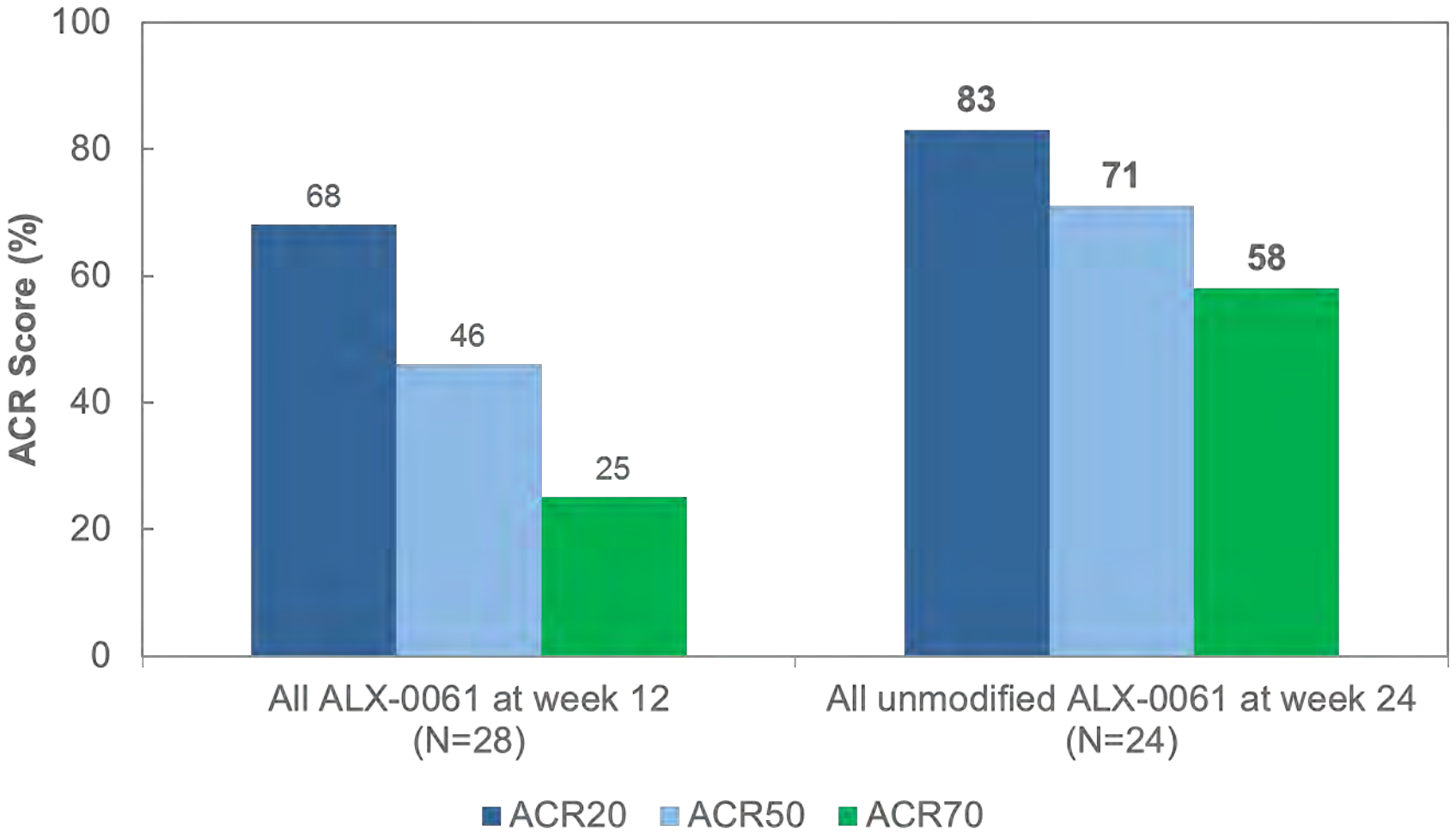
Features	Potential Benefits
Small (26kD) 	• penetrates faster and more effectively into tissues
Targets human serum albumin (HSA)	• prolongs half-life • improved trafficking to inflamed tissue
Monovalent binding	• avoids target cross-linking
Preferential binding of soluble vs. membrane bound IL-6R	• superior benefit/risk profile
Strong affinity to soluble IL-6R	• fast target engagement resulting in fast onset of action
Low immunogenic potential	• improved safety profile
Tailored PK	• extended therapeutic window • convenient dosing and scheduling

ALX-0061 – Phase II study design (MAD)

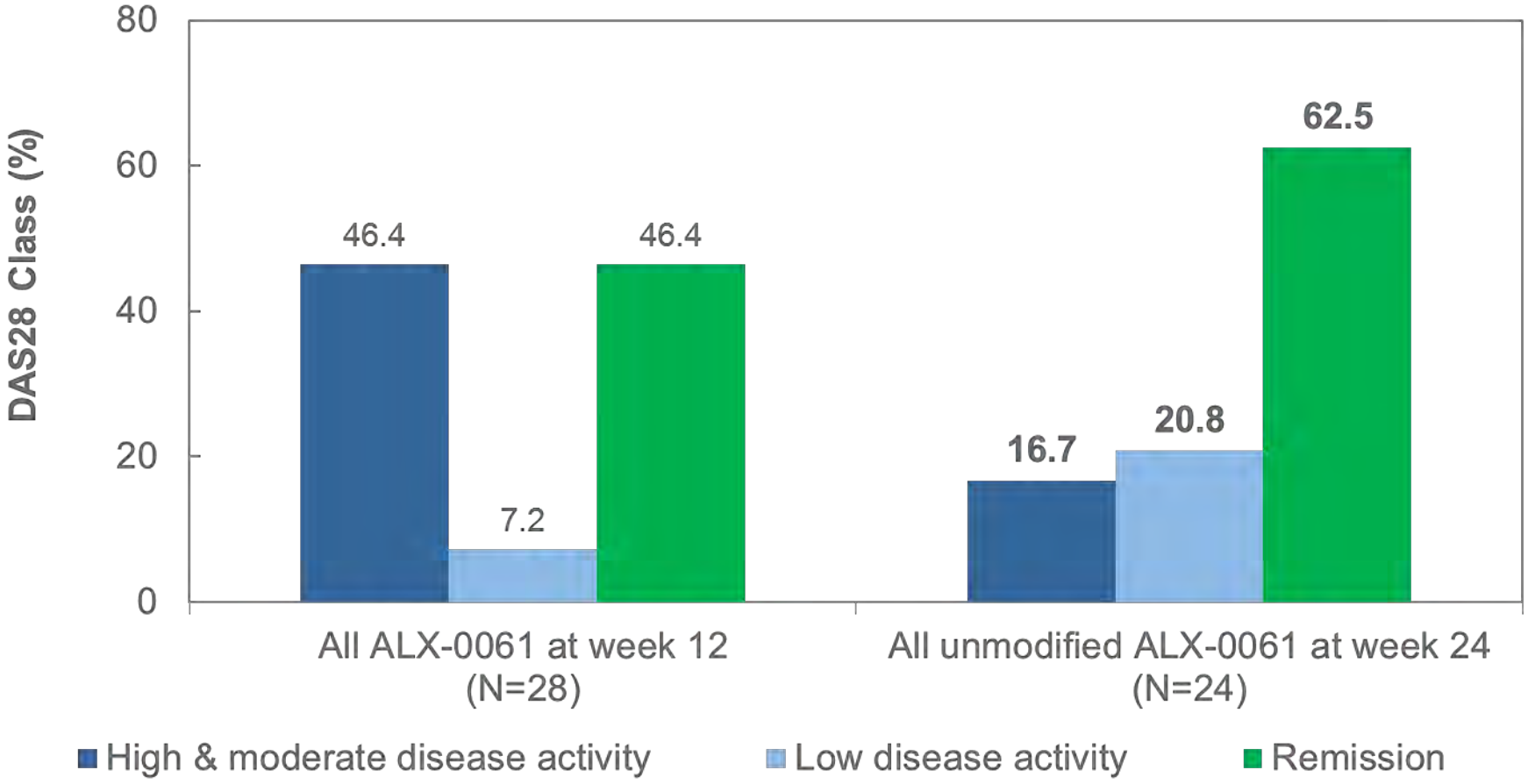


24/28 patients completed the study at their ALX-0061 starting dose

ALX-0061 – ACR scores further improved from week 12 to 24

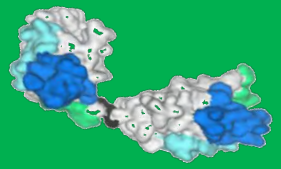


ALX-0061 – strong induction of DAS28 remission



- All DAS28 components contributed substantially to the score
- 20/24 patients achieved low disease activity or remission

Caplacizumab (anti-vWF) – designed to address an unmet medical need in TTP

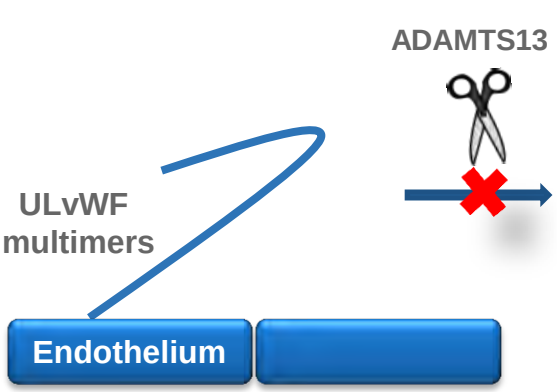


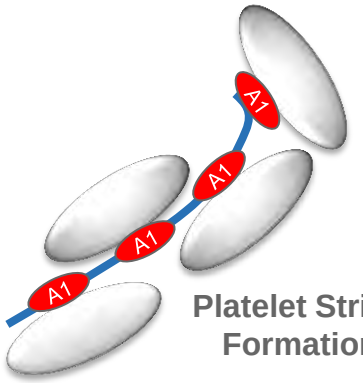
Unique Nanobody Format

Small	Specific	Robust	Modular
not an antibody	high potency towards target	high stability	bivalent interaction with target
no Fc	avoid “off-target” effects	good manufacturability	increased avidity leads to higher potency
rapid distribution and onset of action		*iv* and *sc* formulation	
rapid clearance limits toxicity risk		liquid, lyophilised	

- Orphan Drug designation in US and EU
- Patent term (excluding extensions) will run until 2026
- Potential pivotal Phase II study on-going with the aim to complete recruitment in 2013

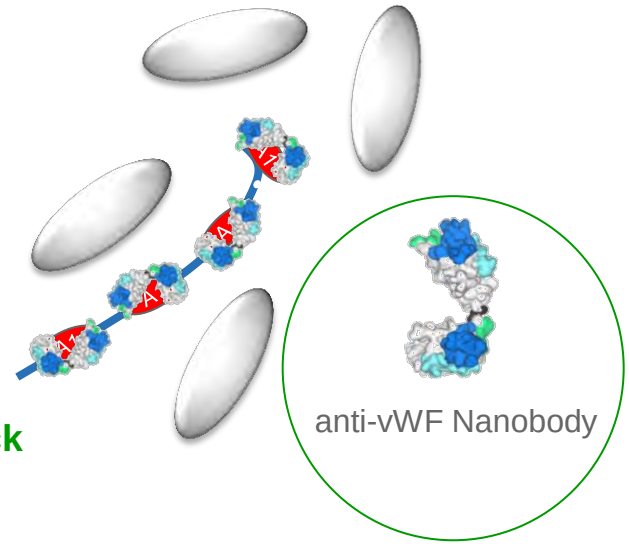
Caplacizumab – blocks the platelet and ULvWF interaction





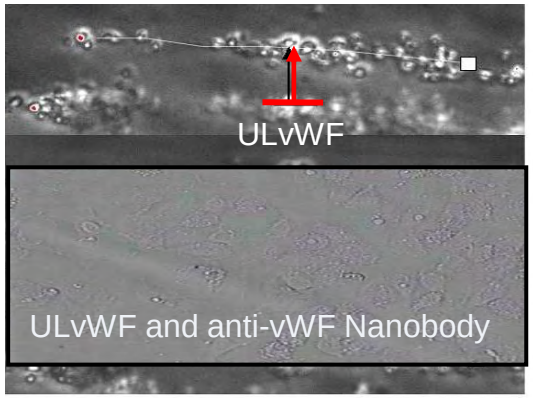
Platelet String Formation

Microthrombi form which block the small blood vessels in thrombotic thrombocytopenic purpura (TTP)



Target for the Nanobody is in the bloodstream, *i.v.* and *s.c.* formulations ensure desired exposure

***Ex vivo* platelet string formation**



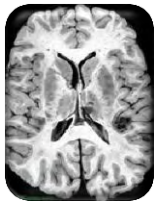
Anti-vWF Nanobody inhibits platelet string formation caused by UL-vWF in plasma of TTP patients

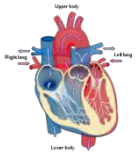
Acquired TTP – an unmet medical need

Healthy active adult

Sudden onset:

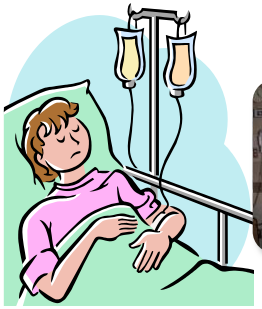
severe fatigue, headache, bizarre behaviour, vertigo, seizures, coma, various other symptoms

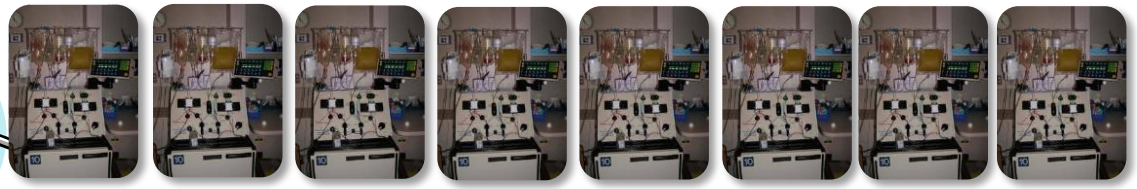




+ caplacizumab

Potentially:
fewer days of PEX
reduction in relapse/exacerbations
improved longer term outcome





Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 ...

Diagnosis of TTP

Daily plasma exchanges in hospital until recovery of platelets count

Respiratory syncytial viral (RSV) infections – unmet need

Duration: 1-2 weeks

***medical cost year after infection**
****risk asthma**




Evolves to distressing symptoms

Symptomatic treatment including inhaled corticosteroid & bronchodilator

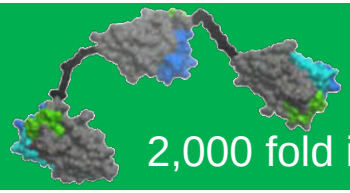
8-20% hospitalised

"RSV infection is the most common cause of lower respiratory tract disease and hospital admission in infants. No effective therapy is available at present. Current prophylaxis with a mAb is expensive and only partially protective. Any new treatment strategy for RSV bronchiolitis is very welcome"

Prof De Boeck, Pediatric Pulmonology

* Shi et al., J Med Econ, 2011; **Sigurs et al., Thorax, 2010; Krishnamoorthy et al., Nature Medicine 2012

ALX-0171 – anti-RSV Nanobody designed for delivery to site of infection



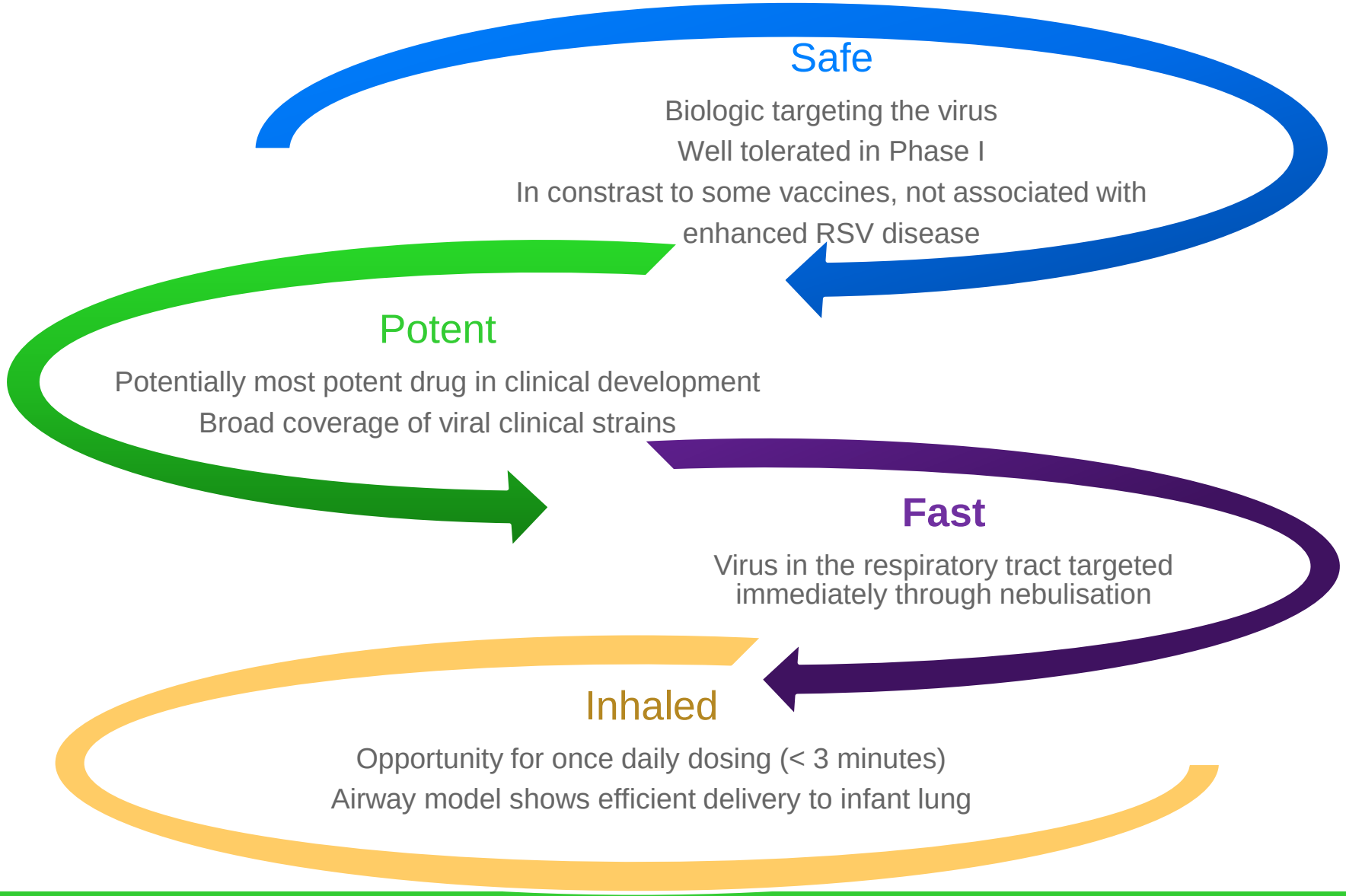
Unique Nanobody Format

2,000 fold increase in potency compared with monovalent structure

Specific	Robust	Convenient
high potency towards the virus	high stability	inhalation
avoid “off-target” effects	efficient nebulisation without loss in potency	opportunity for once or twice daily dosing
well tolerated in Phase I study	potentially reduces viral replication in the lungs	dosing time < 3 minutes

- Patent term (including extensions) will run until 2035

ALX-0171 – potential for transformational treatment of RSV



ALN-RSV01: Alnylam (PhII b completed to treat progressive bronchiolitis obliterans syndrome; primary endpoint not met); MDT637: Microdose (PhI completed to treat RSV)

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