Challenges & opportunities of anti-D development in an evolving landscape

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- Former employee of CSL/CSL Behring (including shareholder via LTI)
- Former employee of Octapharma

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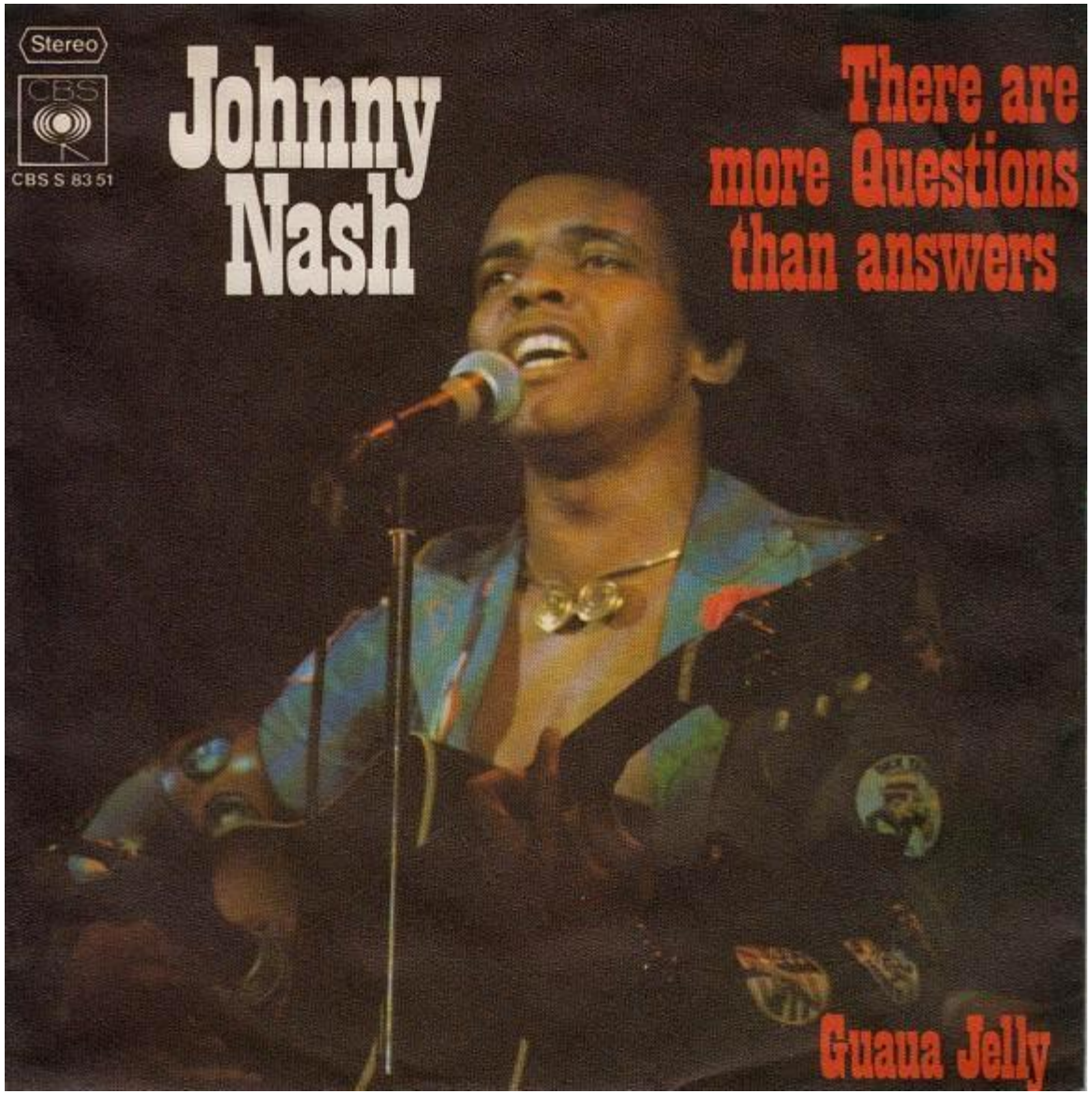
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Johnny Nash
There are more Questions than answers
Guava Jelly


JOHNNY NASH
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I can see clearly now
How good it is

Summary and plan

In the 1960s, prophylaxis against RhD allo-immunization was introduced, and this has reduced foetal and neonatal morbidity and mortality due to HDFN dramatically

Anti-D immunoglobulin is included in the Union list of critical medicines (critical for EU healthcare systems to function properly).
Several key vulnerabilities in the supply chain of anti-D Ig have been identified

Alternatives to plasma-derived anti-D immunoglobulins were researched since more than 20 years, without major recent advancement, multiple challenges persiste

Anti-D Monoclonal antibody: Roledumab

(LFBR593)

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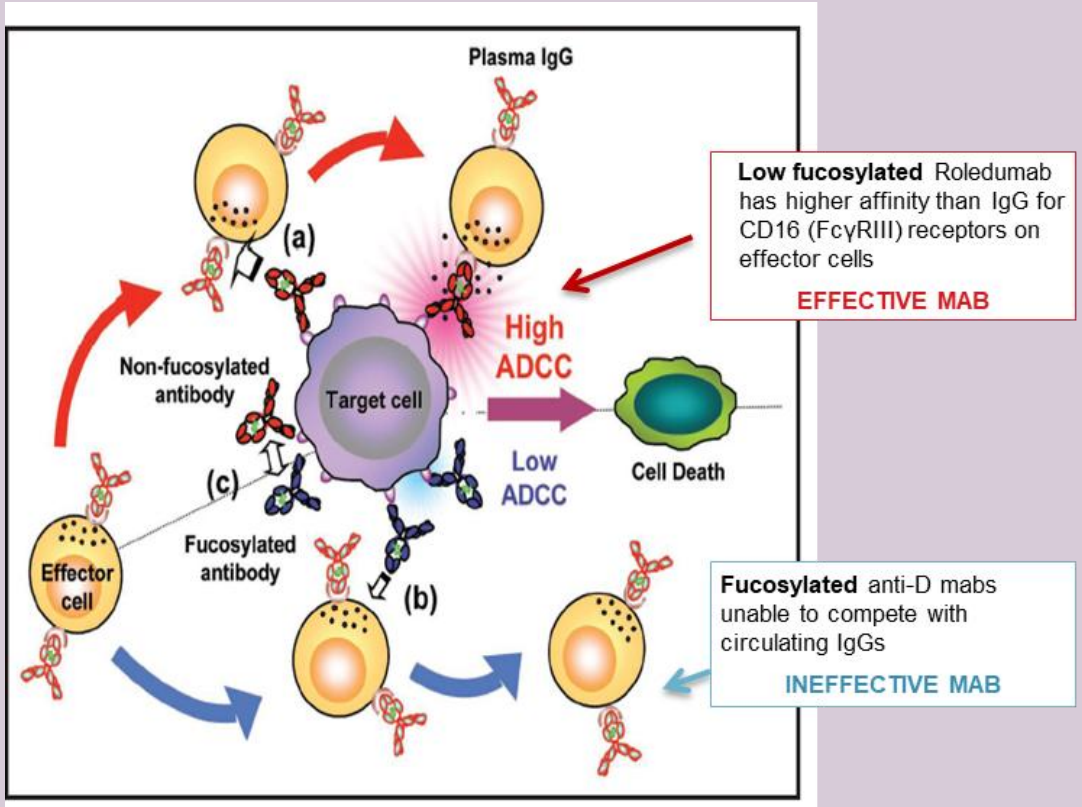
A human recombinant IgG1 with a glyco-engineered Fc fragment triggering higher ADCC/Phagocytosis for the prevention of RhD-alloimmunization

Mechanism of action



- When a RhD negative individual is exposed to RhD positive Red Blood Cells (RBC) (pregnant women, transfused patient), anti-D immunoglobulins treatment clears the incompatible RBCs without alerting the subject's immune system, thus prevent them from being immunized to RhD antigen, one of the main causes, during pregnancy, of hemolytic disease of fetus and newborn, a potentially severe, disabling and life-threatening condition

Key features

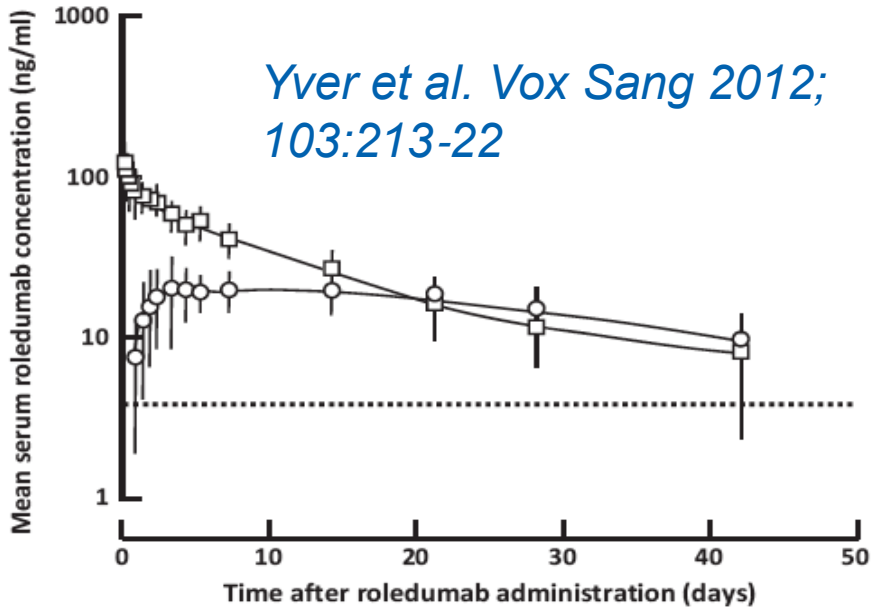
- **Human recombinant anti-Rhesus D monoclonal IgG1 antibody**
- mAb sequence **cloned from immunized donor lymphocyte**
- Produced by **YB2/0 rat myeloma cell line**
- **Optimized glyco-engineered Fc fragment** (low fucose) with strong binding to CD16 receptors of effector cells triggering **higher ADCC/Phagocytosis**
- **Mechanism of action (MoA): macrophages mediated phagocytosis**
- **Strong affinity to RhD antigen** and to a broad spectrum of RhD-Variants

Siberil et al. Clin Immunol 2006;118:170-9
Béliard et al. Brit J Haematol 2008; 141:109-19
Rouby et al. Mabs 2020; 12:e1781743

Phase I (ADNC-701): PK/safety - Bioavailability IV/IM

N=46 HEALTHY RHD-NEG VOLUNTEERS)

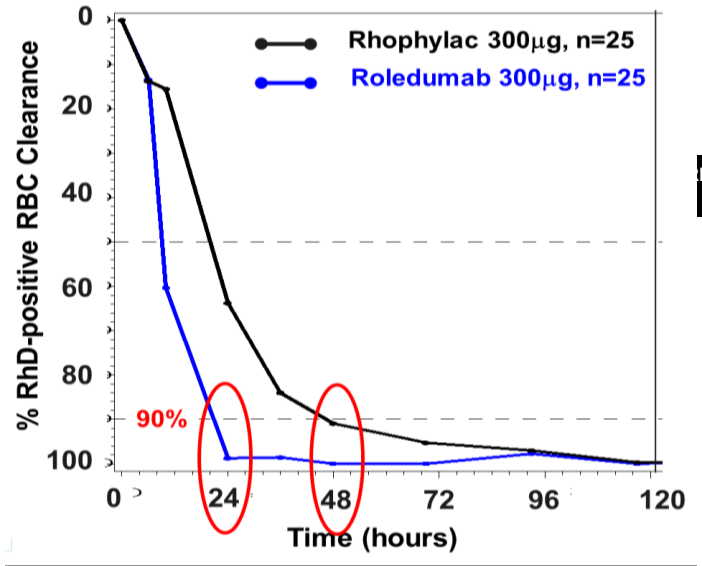
- **Roledumab PK parameters (300µg IV and IM) are similar to plasma derived anti-D (Rhophylac 300µg IV and IM)**



Phase II (ADNC-726) - Proof of Concept Study

RHD- HEALTHY VOLUNTEERS CHALLENGED WITH RHD+ RBC

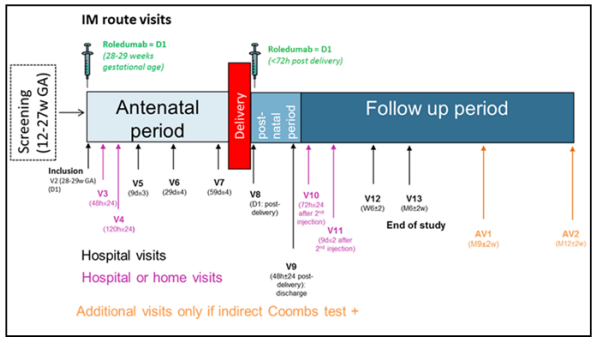
- **<u>Efficacy</u>: Roledumab exhibits a faster RhD-positive RBC clearance than plasma anti-D (IV and IM 300µg dose) – No immunization in any of the Roledumab groups (vs 1 immunization in Rhophylac 300µg IV group)**
- **<u>Safety</u>: Single IV and IM doses of up to 300 µg Roledumab administered in healthy RhD-negative subjects who had previously received 15 mL of RhD-positive RBCs were safe and well tolerated in this clinical study. There were no Adverse Events (AEs) of 'severe' intensity and no withdrawals due to AEs. All AEs following Roledumab IV or IM injection had resolved at the end of the study**

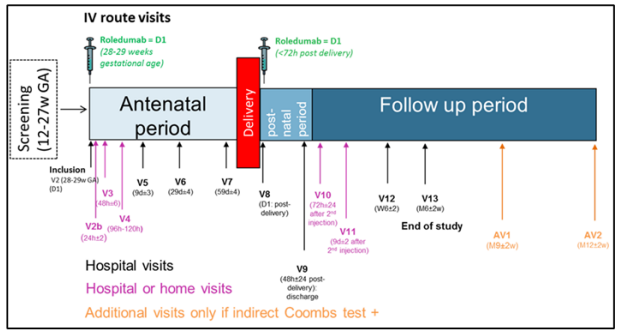


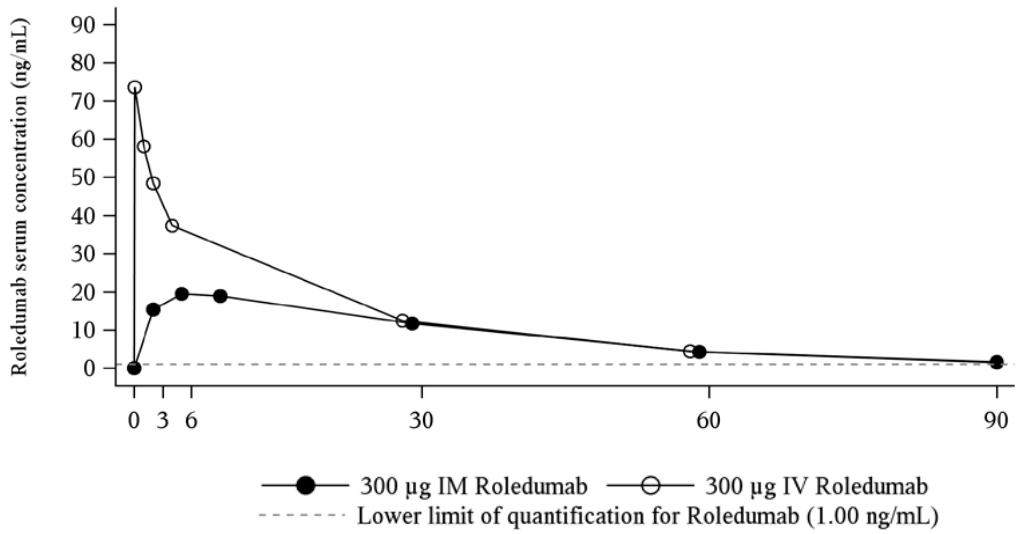
Phase II (ADNC-1301) - 1st in Pregnant Women

DOSE CONFIRMING PK/SAFETY STUDY- IM 300µg group (n=26) – IV 300µg group (n=36)

Design	• Phase 2b, Multicenter, Open-label, Non-randomized
Treatment	**Antenatal prophylaxis:** • 1 single dose 300 µg IM/IV at 28 or 29 weeks of gestation **Postnatal prophylaxis:** • 1 single dose 300 µg IM/IV within 72 hours of delivery of an RhD-positive infant • In case of sensitizing event
Primary endpoint	• PK in mother blood
Secondary endpoints	• Safety, Efficacy, Immunogenicity, Concentration in cord blood and in breast milk





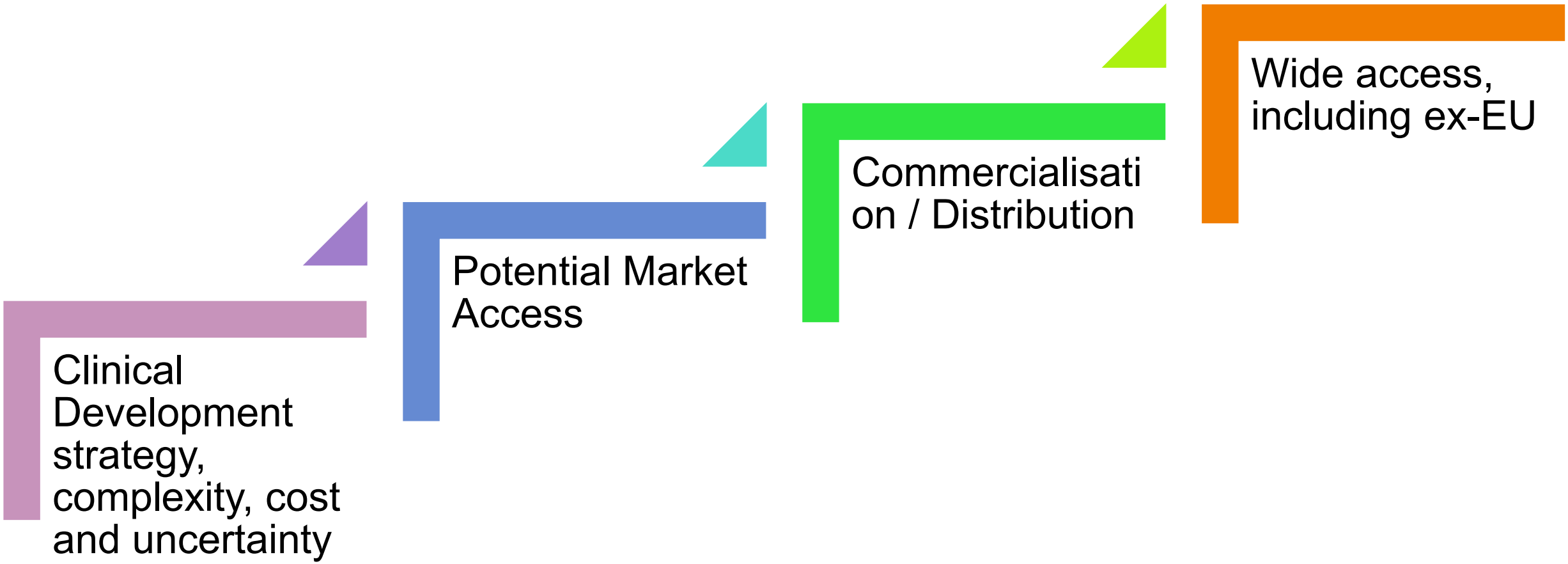


- **PK/safety profile comparable to plasma anti-D: no hemolytic reaction in fetus/newborn nor serious adverse events related to product, no immunogenicity reaction (no anti-drug antibodies), no significant Roledumab milk and transplacental passage observed**
- **Efficacy: no treatment failure (i.e no alloimmunization), efficient product coverage until delivery**

Roledumab status to date (development on hold)

- Human recombinant anti-Rhesus D monoclonal IgG1 antibody
- Optimized glyco-engineered Fc fragment (low fucose) with strong binding to CD16 receptors of effector cells triggering higher ADCC/Phagocytosis
- Non-Clinical : Documented Pharmacological Profile
- Product: Structural & Analytical Characterization
- Manufacturing : Optimized process available, further refinements ongoing
- Ready-to-use prefilled syringe (1mL, 300µg dose for IV/IM route)
- Phase I Study Results (Healthy Volunteers) - First in Man
- Phase II Study Results (Healthy Volunteers) - Proof of Concept
- Phase IIb Study Results (Pregnant Women) - First in target Population

Major challenges



Major ~~challenges~~ opportunities?

Innovative clinical / regulatory approach?

Non-commercial model?

Proactive engagement with payers?

Alternative sources of funding?

Clinical Development strategy, complexity, cost and uncertainty

Commercialisation / Distribution

Potential Market Access

Wide access, including ex-EU

Thank you !

Any feedback?
Reach out !

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