# Biography and Contact Information

- Head of Bioassay Development and Operations at Bill & Melinda Gates Medical Research Institute (Gates MRI)
  - "Our bottom line: lives saved"
- Previously in bioanalytical and biomarker roles at EMD Serono, Biogen, Bristol-Myers Squibb, BioMarin Pharmaceutical Inc.
- Coauthor on 2 manuscripts in the Compendium of Immunogenicity Risk Assessments
- 2021 Co-Chair of AAPS Bioanalytical Community
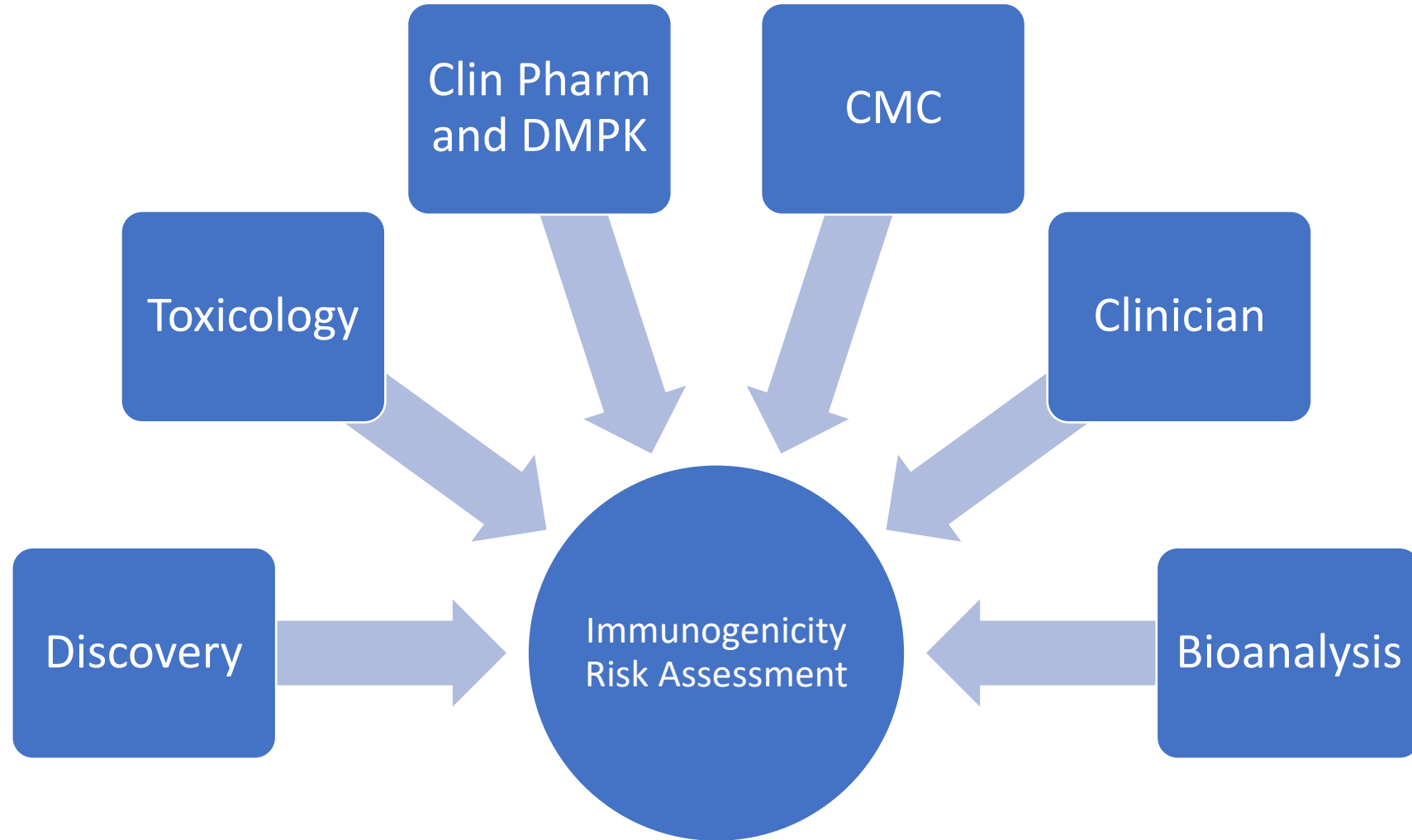- AAPS Communities Top Contributor
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Outline

- Introduction to Immunogenicity Risk Assessment

- Case Study for RSM01 Immunogenicity Risk Assessment

- Conclusions

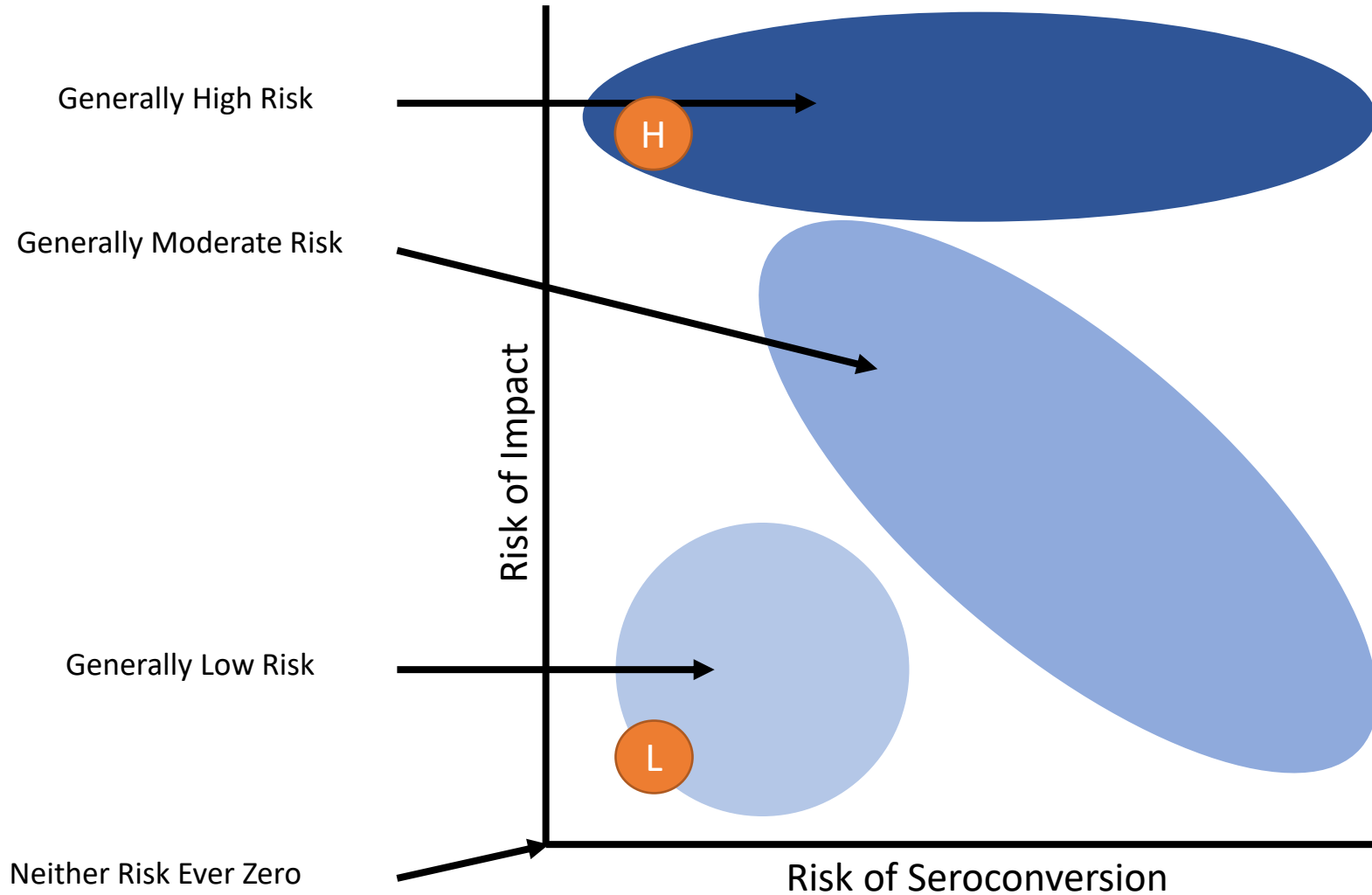# Immunogenicity Risk Assessment is a Continuous Process
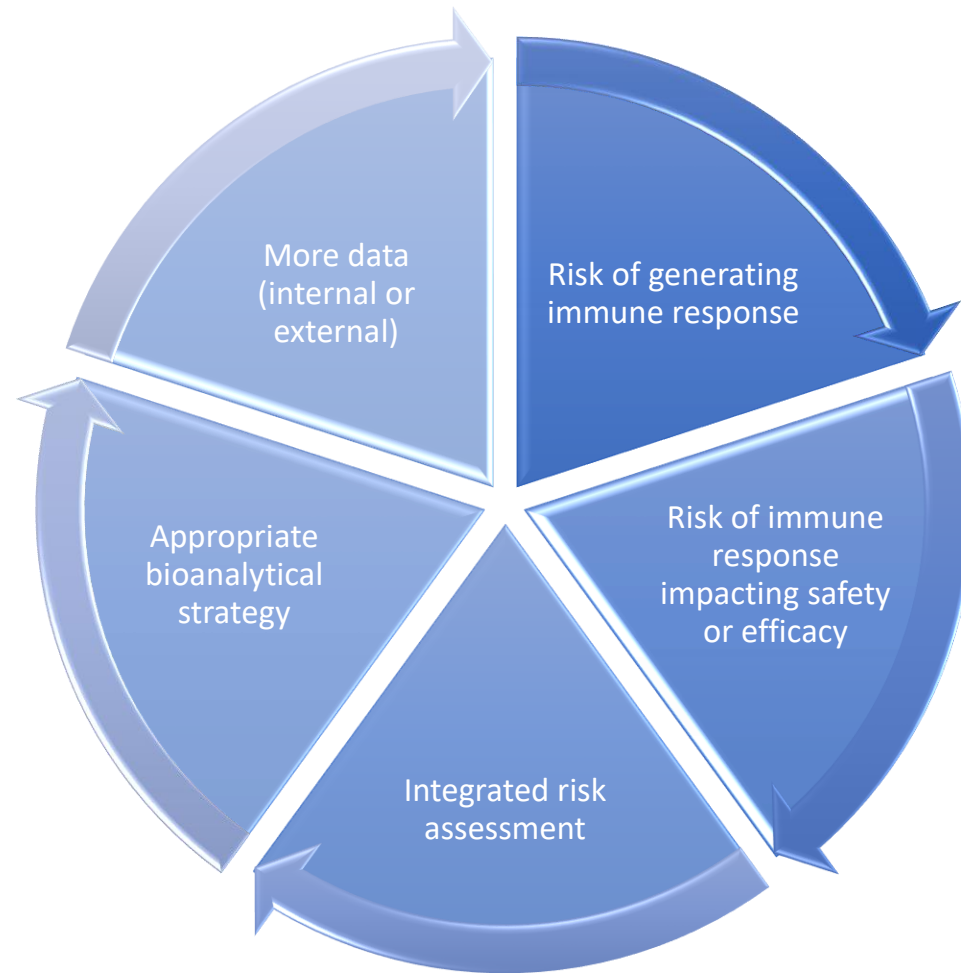
Immunogenicity Risk Assessment is a Collaboration Across Expertise

Separate Risks of Seroconversion and Immunogenicity Impact

Same Seroconversion Risk Can Have Different Risk of Impact

Immunogenicity Risk Assessment is Part of Overall Risk/Benefit Assessment

RISK   **BENEFIT**

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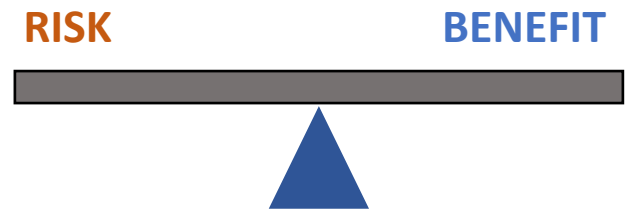
Dynamic Risk Assessment: Level May Increase/Decrease over Program

1. Initial assessment during discovery (assumed impact on PK/PD)

2. A nonclinical safety finding potentially related to ADA

3. Phase 1 study determined that nonclinical finding was not observed clinically

4. Registrational studies clarify risk of seroconversion and no observed PK/PD effect
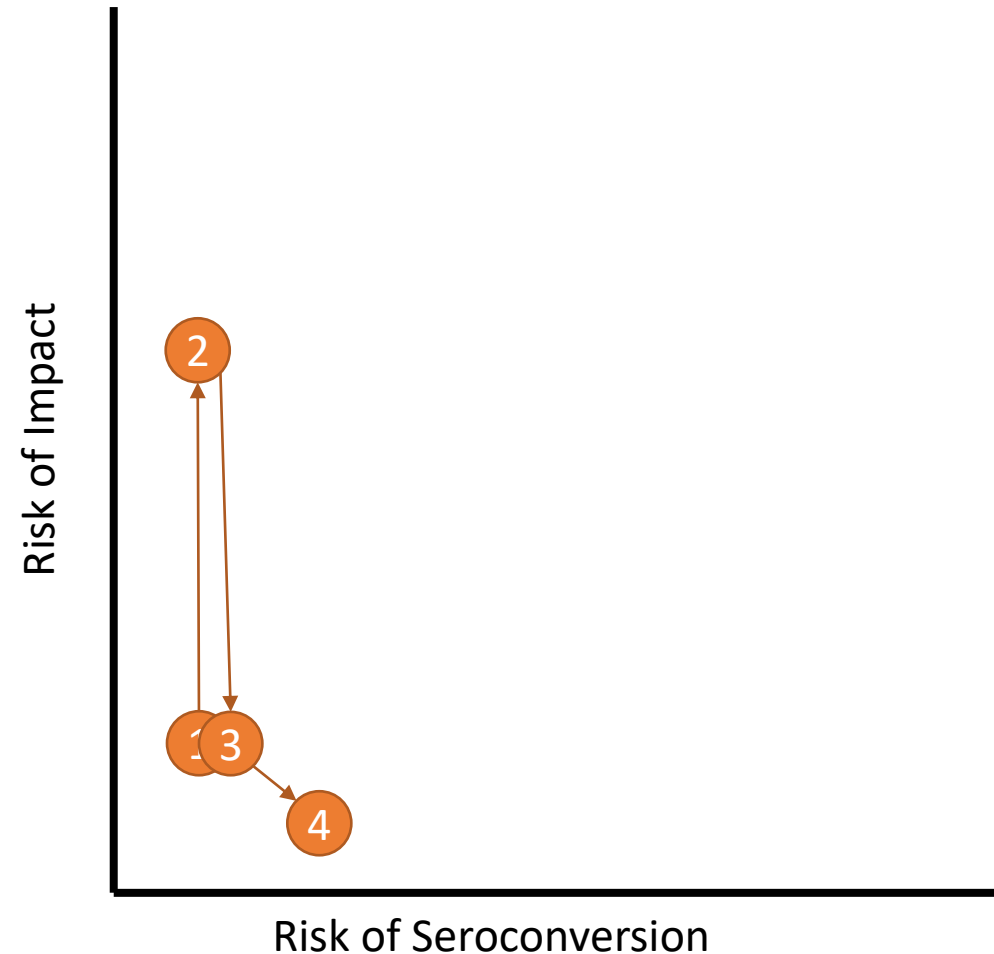
Bioanalytical Strategy Tied to Immunogenicity Risk Assessment

- Assays and sampling time points are the last piece of the risk assessment to demonstrate how the risks are being measured in the clinical development plan

- Timing considerations
  - Dosing interval
  - Seroconversion kinetics

https://opentextbc.ca/biology/chapter/23-2-adaptive-immune-response/
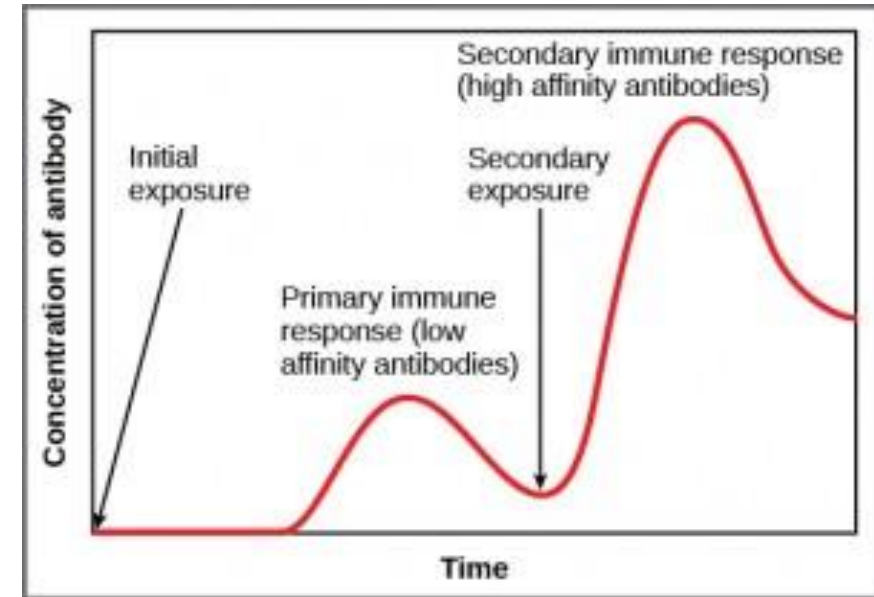
RSM01: Prevention of Lower Respiratory Tract Infection Resulting from Respiratory Syncytial Virus

https://rsvgold.com/
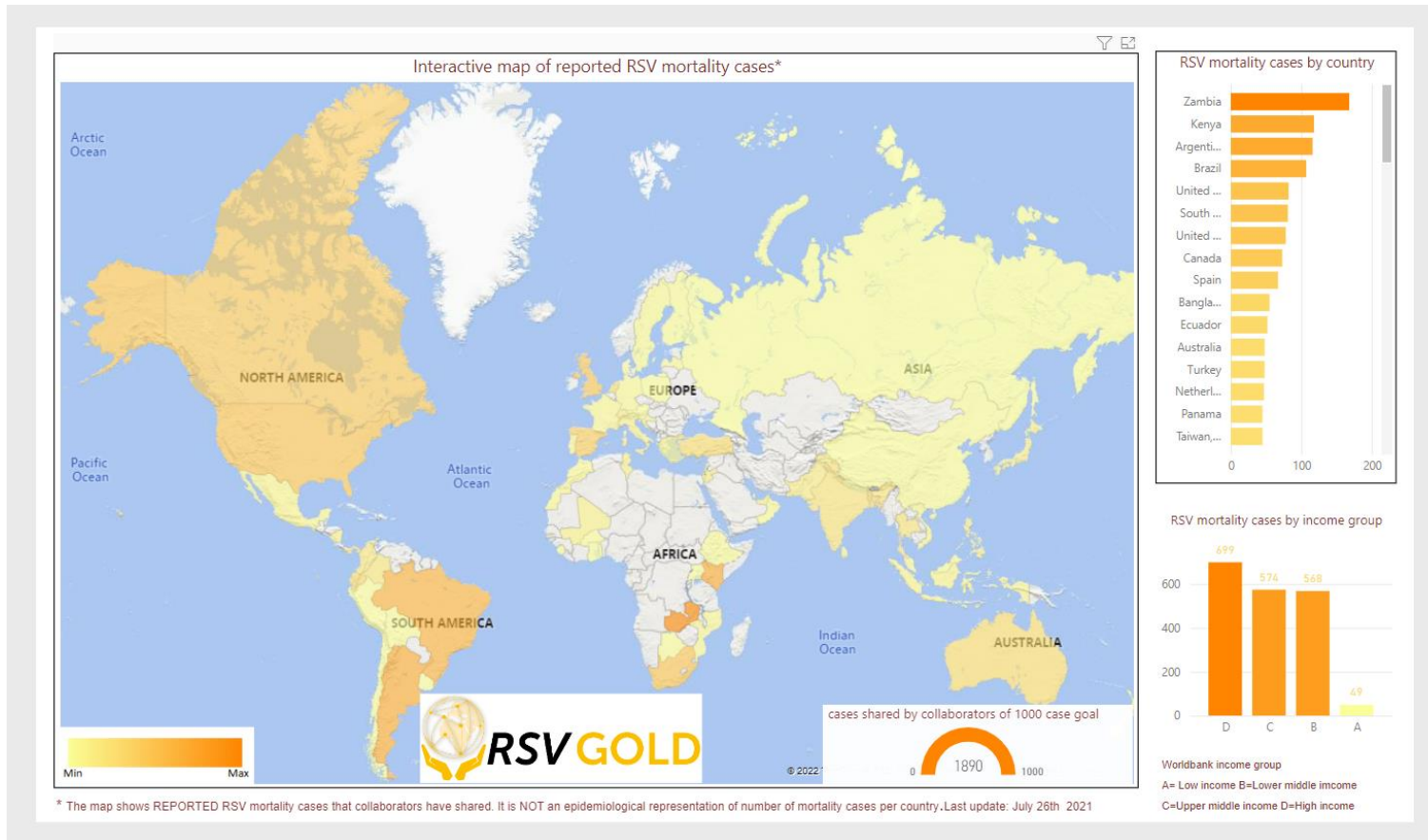
- Respiratory Syncytial Virus (RSV)
  - Symptoms often limited to "common cold"
  - Progression to Lower Respiratory Tract Infection (LRTI) risky for infants with underdeveloped lungs
  - Leading cause of global infant hospitalization
  - Vaccines not effective in infants
  - https://www.resvinet.org/

RSM01: Candidate to Prevent of Lower Respiratory Tract Infection Resulting from Respiratory Syncytial Virus

- RSM01 is a candidate molecule developed with funding from Bill & Melinda Gates Foundation

- RSM01 Use Case
  - Passive immunization covering infancy prior to future childhood vaccination (at an effective age)
  - Prevent disease in most vulnerable first 6 months of life
  - Single dose to cover RSV season for infants

- Landscape
  - Synagis® (palivizumab):
    - monthly treatment for high risk infants
    - https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/palimed102302LB.pdf
  - Beyfortus (nirsevimab)
    - Second generation with YTE half-life extension
    - https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf

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Potential Consequences of Immunogenicity in Patients

Potential consequence	Relevance for RSM01
Induction of ADA's that cross-react with endogenous counterparts	Not relevant for RSM01: effective immune tolerance for human germ-line sequences in human IgG1; no endogenous counterparts for non-germline sequences in RSM01
Allergic-type hypersensitivity / anaphylaxis	Not relevant for RSM01: no allergenic motifs identified in humanized IgG1 expressed in CHO cells
Immune complex-related hypersensitivity	Possibly relevant if non-human germline sequences in RSM01 VH or VL regions have capacity to induce T-cell-dependent humoral immune responses of sufficient magnitude to influence a second or subsequent administration. However, unlikely to be relevant for single dose prophylactic administration.
Reduced pharmacodynamic (RSV-neutralizing) response	
Altered pharmacokinetics	
Compromise of subsequent treatment with related products	Highly unlikely if treatment-emergent immune response was directed against the unique CDR sequences of RSM01
Uncertain long-term clinical impact	Possibly relevant for intermittent (seasonal) prophylactic use

Intrinsic Immunogenic Potential and Product Quality

Characteristic	Overview
Proportion of Human Sequence	Close to VH3-23 and VK3-11 germline with half-life extension in HC constant region
Immunogenic Motifs	In silico prediction (https://www.iedb.org/) • CD4 T-cell epitope prediction (IEDB recommended; 50% Threshold) http://tools.iedb.org/CD4episcore/ • MHC Class II binding (7-allele HLA Reference set) http://tools.iedb.org/mhcii/
Aggregation	< Limit of quantitation Stability studies ongoing at time of IND
Post-Translational Modifications	One N-glycosylation site
Process Impurities	Below pre-specified limits
Host Cell Line for Manufacturing	Chinese Hamster Ovary

Mode of Action/Systems Biology/Subject Related Factors

Question	Summary
Is the target population likely to be fully immune competent, or could subjects be immunocompromised or receiving concomitant immune-suppressive medication?	Immunogenicity of a single intra-muscular administration of RSM01 will be evaluated in the most sensitive population, i.e. healthy adults, prior to administration to newborn infants. Probability of an adaptive immune response to RSM01 in newborn infants may be reduced compared to that in adults by a decreased reactivity of both the innate and adaptive immune systems.
Could the location / function of the target influence extent of antigen uptake and presentation to alter an adaptive immune response?	Neither the nature of the RSV target antigen nor the mode of action or extended half-life of RSM01 are anticipated to enhance risk of immunogenicity of RSM01.
Could the viral antigen load or disease pathology influence the immunogenicity risk profile?	Although RSV disease severity may be related to viral antigen load, neither viral antigen load nor disease pathology are anticipated to represent influential variables for immunogenicity of a prophylactic anti-RSV mAb.
Is there any potential for cross-reactivity of anti-RSM01 antibodies with endogenous human antigens?	Probability of induction of an autoreactive immune response by a single administration of RSM01 is considered to be negligible.

Conditions of Use –
Clinical Development Plan and First in Human (FIH) Phase 1 Study

- Single dose administration to healthy adults using an escalating dose scheme, with adequate monitoring for adverse reactions, will minimize probability of safety-related risks while optimizing sensitivity to detect immunogenicity.

- The proposed exclusion criteria are appropriate to avoid administration to subjects with highest risk of immune-related adverse events, or who may be immunocompromised to an extent that could bias interpretation of immunogenicity.

- There is no identified clinical risk that would merit pre-medication for reduction of incidence or severity of acute hypersensitivity reactions.

- The IM route proposed for the RSM01-101 study is relevant for the intended prophylactic use of RSM01.

- The IV route of administration will enable evaluation of tolerability of higher dose levels in healthy adults, but is not expected to increase probability of clinically impactful administration following a single dose of RSM01.

Detection of Treatment-Induced Humoral Immune Responses to RSM01

Method	Fit for Purpose
Anti-drug antibodies (ADA)	Detect 50 ng/mL PC in presence of 500 µg/mL RSM01 Validate adult cut point factor pre-study Infant cut point factor to be determined in-study
Neutralizing anti-drug antibodies (nAb)	Not planned in early clinical development • Low probability of seroconversion • Pharmacodynamic assay • Bank ADA positive samples regardless
RSM01 (PK assay)	Detection below anticipated clinically efficacious concentration
RSV neutralization ex vivo	Pharmacodynamic assessment

Detection of Treatment-Induced Humoral Immune Responses to RSM01

Dose Escalation	Study Visit / Day											
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Discon visit
Activities	D1 ±0d	D2±0 d	D4±1 d	D6±1 d	D8 8-10	D15±3d	D29 29-35	D61±7 d	D91±7 d	D121±7 d	D151±7d	
PK	X	X	X	X	X	X	X	X	X	X	X	X
ADA	X					X	X	X	X	X	X	X
Serum RSV nAb levels	X								X		X	X

Dose Expansion	Study Visit / Day								
	V1			V2		V3		V4		V5	Discon visit
Activities	D1 ±0d			D8 8-12		D29 29-35		D91±7 d		D151±7d	
PK	X			X		X		X		X	X
ADA	X					X		X		X	X
Serum RSV nAb levels	X							X		X	X

Summary of Immunogenicity Risk Evaluation and Mitigation

Potential Consequences	Risk Evaluation	Risk Mitigation in FIH Study

Immune complex-related hypersensitivity reactions	• Monitoring of ADA at baseline and following single dose IM or IV administration
	• Assessment of temporal relationship of acute hypersensitivity reactions to pre- & post-treatment ADA signals (positive/negative status & titer)
		• Cautious single administration, dose escalation cohort design
		• Exclusion of subjects at highest risk of immune-related adverse reactions
		• Close surveillance for treatment-related adverse events:
		   o For the Dose Escalation Phase Cohorts to after completion of Day 2 assessment (1 overnight stay).
		   o On any given day, participants will be dosed at least 2 hours apart regardless of mode of administration (IM or IV). The 2-hour wait time between IV infusions is to begin at the end of the previous infusion.
		• Independent Data Monitoring Committee (IDMC) will make dose escalation recommendations based on accumulating safety and any available PK data
		• In addition, an observed AE of special interest (AESI) will also trigger a pause in enrollment and in participant dosing, until the IDMC reviews all available data.
		   o AESIs are 1) anaphylaxis or hypersensitivity reactions and 2) infusion reactions resulting permanent discontinuation of infusion in IV recipients.

Reduced pharmacodynamic (RSV-neutralizing) response	Assessment of relationship of pre- & post-treatment ADA signals (positive/negative status & titer) to • RSM01 PK and • RSV neutralizing capacity	
Altered pharmacokinetics		
Uncertain long-term clinical impact	• Monitoring of ADA levels for up to 151 days following single dose IM or IV administration	

Summary of Immunogenicity Risk Assessment

The probability of induction of a clinically impactful immune response to a single IM or IV dose of RSM01 to healthy adults or healthy infants is considered to be low. The first-in-human study to be performed in healthy adults has been designed to have optimal sensitivity to detect an impact of pre- or post-treatment ADA on the relevant PK, PD and safety measures. These provisions are considered fully adequate to assess consequences of immunogenicity associated with RSM01 for single-dose prophylactic administration.

Updating the Immunogenicity Risk Assessment

FIH Ongoing

- Safety, Tolerability, and Pharmacokinetics of RSV Monoclonal Antibody RSM01 in Healthy Adults
- [NCT05118386](NCT05118386)

Next Steps

- Update risk assessment upon completion with observed clinical data
- Update risk evaluation and mitigation strategy for subsequent clinical development program

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Conclusions

- Start with potential impact if anti-drug antibodies form in a patient

- Pull together data to inform risk of seroconversion from intrinsic factors, mechanism of action, target population, etc.

- Describe how risks of seroconversion and risks of potential consequences will be monitored in the clinical program

- Implement plan and update as new information about risks emerge (included measured seroconversion rates)

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RSM01 Development Team

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