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Implementing a patient-centric sampling strategy in the global clinical development of RSM01 (Anti-RSV mAb)

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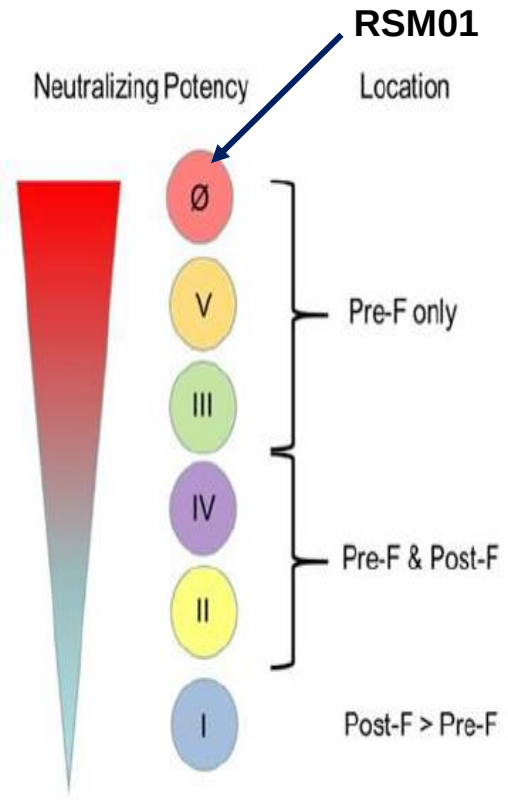
Respiratory Syncytial Virus (RSV) is a major global health concern, primarily affecting young children

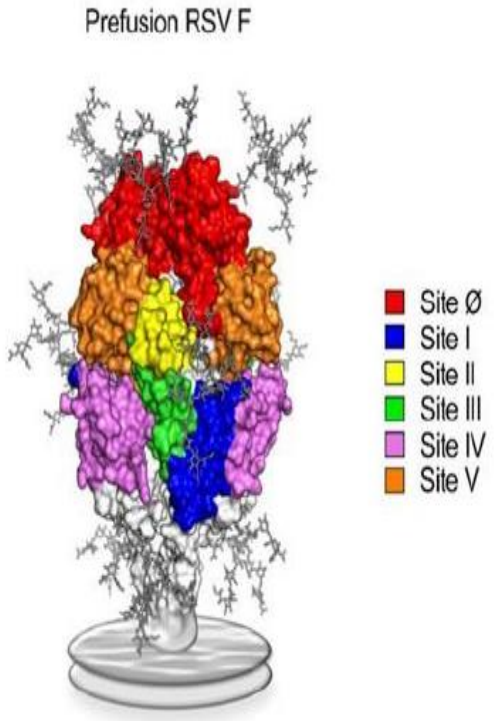
- In 2015, an estimated 1.4 million hospital admissions were due to RSV
- There were approximately 273,000 in-hospital deaths among infants less than 6 months old, and more than 99% of these deaths occurred in developing countries [Shi 2017]*
- There is an urgent need for affordable, safe, and effective prevention against RSV, especially in low- and middle-income countries (LMICs)
- The goal of the RSM01 development program is to develop a safe and effective mAb to prevent RSV disease in infants, with a focus on accessibility in LMIC

*DOI: 10.1016/S0140-6736(17)30938-8

RSM01: A long-acting, potent neutralizing RSV mAB

- Fully human IgG1 mAb
- Targets antigenic site zero of the prefusion F protein (a region considered to be highly neutralization sensitive).
- Acts by binding to and inhibiting the pre-fusion form of RSV glycoprotein F on the surface of the virus, blocking a critical step in the membrane fusion process.
- YTE mutation in Fc region increases serum $t_{1/2}$
- Potential for a single dose for RSV season coverage





Benefits for using mirosampling in the RSM01 global development program*

Ethical Benefits:

- Obtaining samples from infants
- Collection of samples in a closer timeframe to a clinical event
- Freeing-up blood volume to collect additional samples

Improved Patient Experience:

- Sample collection in settings more convenient to the patient
- Limiting disruption to normal life for clinical study subjects
- Less invasive than venipuncture

Direct Cost Savings:

- Ambient Temperature Sample Shipments:
- Reduced Shipping Costs

Indirect Cost Savings:

- Less Clinical Staff Needed for Blood Sample Collection
- Improved Clinical Trial Recruitment and Retention

Process Simplicity:

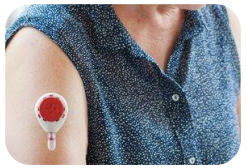
- Minimized On-Site Processing
- This simplification reduces labor, resources, and potential error sources.

*Spooner, 2019, DOI: 10.4155/bio-2019-0041

Patient-Centric Blood Collection

Capillary blood rather than venous

- Capillary blood suitable for lower volume collection
  - Heel prick standard for infants
  - Options to collect liquid to process to plasma/serum
  - Options to collect whole blood
- Potential to use dried blood for all PK in program



Tasso

TAP

BD Microtainer

Capitainer

Hemapen

Mitra

RSM01 PK Implementation (VAMS®)

- Support microsampling as the **primary** matrix for RSM01 pharmacokinetics in **clinical** development program
- Analytical Method Development
  - Use volumetric absorptive microsampling (VAMS) with plastic substrate (20 µL)
  - 100% recovery versus whole blood spike
  - Ongoing stability studies, but at least 6 months at room temperature (22°C)
- Clinical replication study within RSM01-101 to provide bridging data
  - Enable modeling to include nonclinical and nirsevimab serum data
  - Fully matched profiles for venous serum vs. capillary blood VAMS
    - Far exceeds the requirements for a bridging study
    - Enables comparison of PK parameters in addition to raw drug concentration from samples

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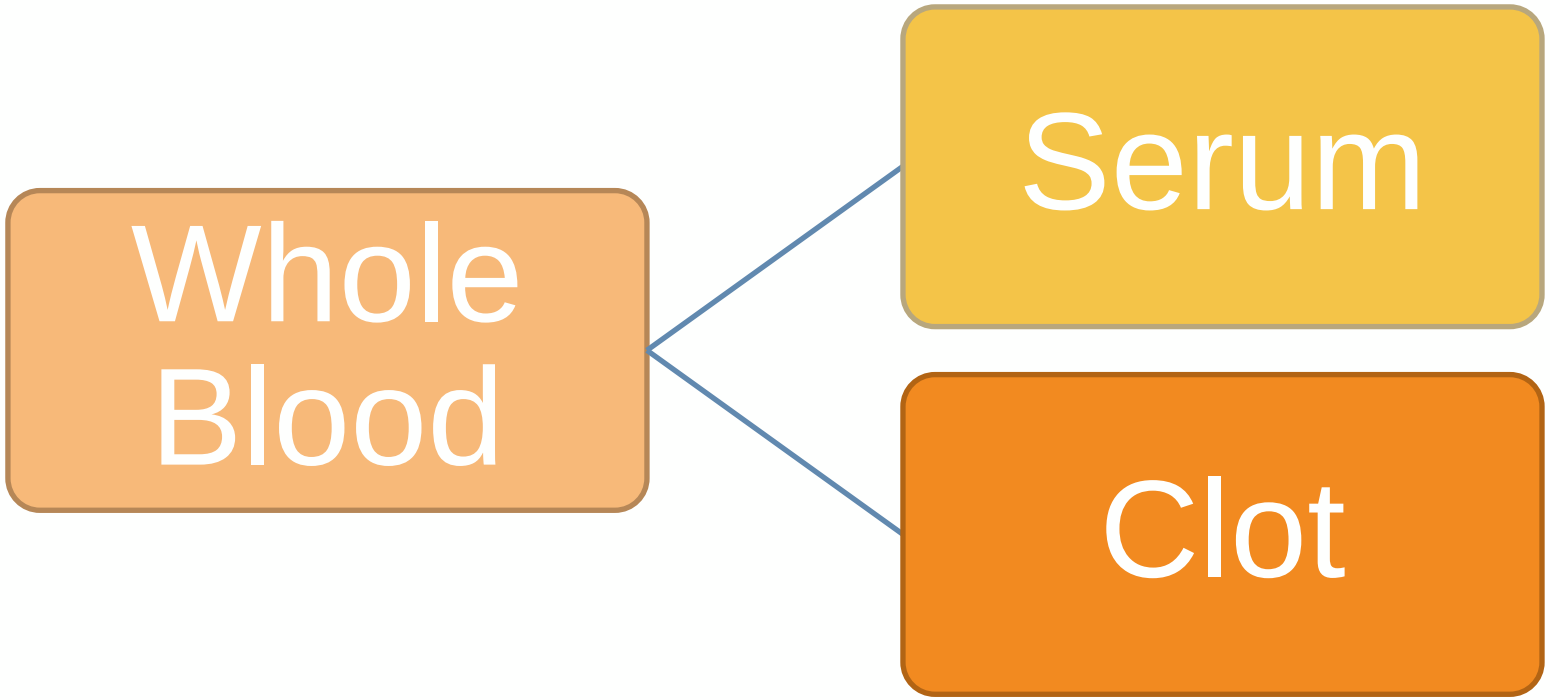
Monoclonal Antibody Partitions to Serum



- Serum concentrations will be higher than whole blood
  - Hematocrit can approximate the partition factor
- Calculate conversion to include serum data sets in modeling
  - Other anti-RSV monoclonals
  - Nonclinical efficacy models

Gates MRI-RSM01-101 Study Design

Phase 1 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and PK of Single Ascending Doses of RSM01in Healthy Adults

Dose Escalation Phase

Cohort 1
300 mg IV
RSM01, n = 6;
PBO, n = 1

Cohort 2
300 mg IM
RSM01, n = 6;
PBO, n = 1

Cohort 3
1000 mg IV
RSM01, n = 6;
PBO, n = 1

Cohort 4
3000 mg IV
RSM01, n = 6;
PBO, n = 1

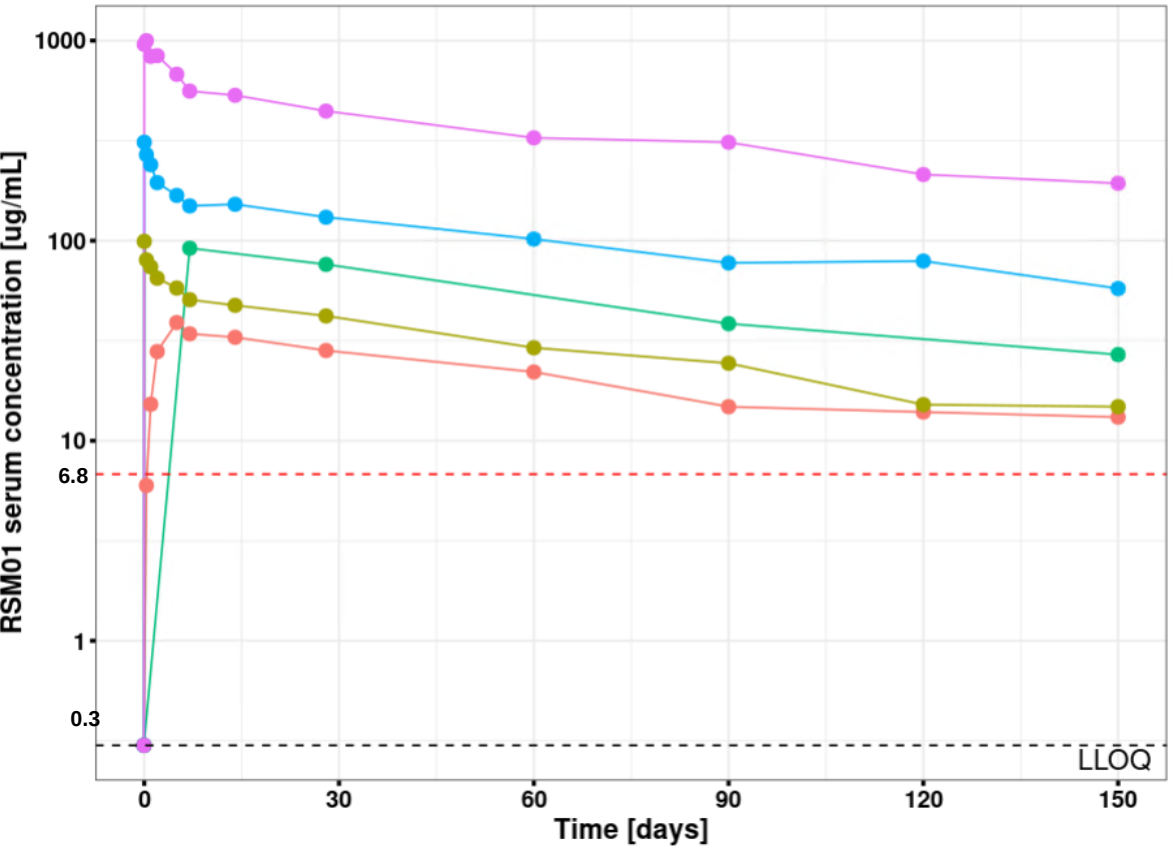
Dose Expansion

Cohort 5
600 mg IM
RSM01, n = 24;
PBO, n = 4

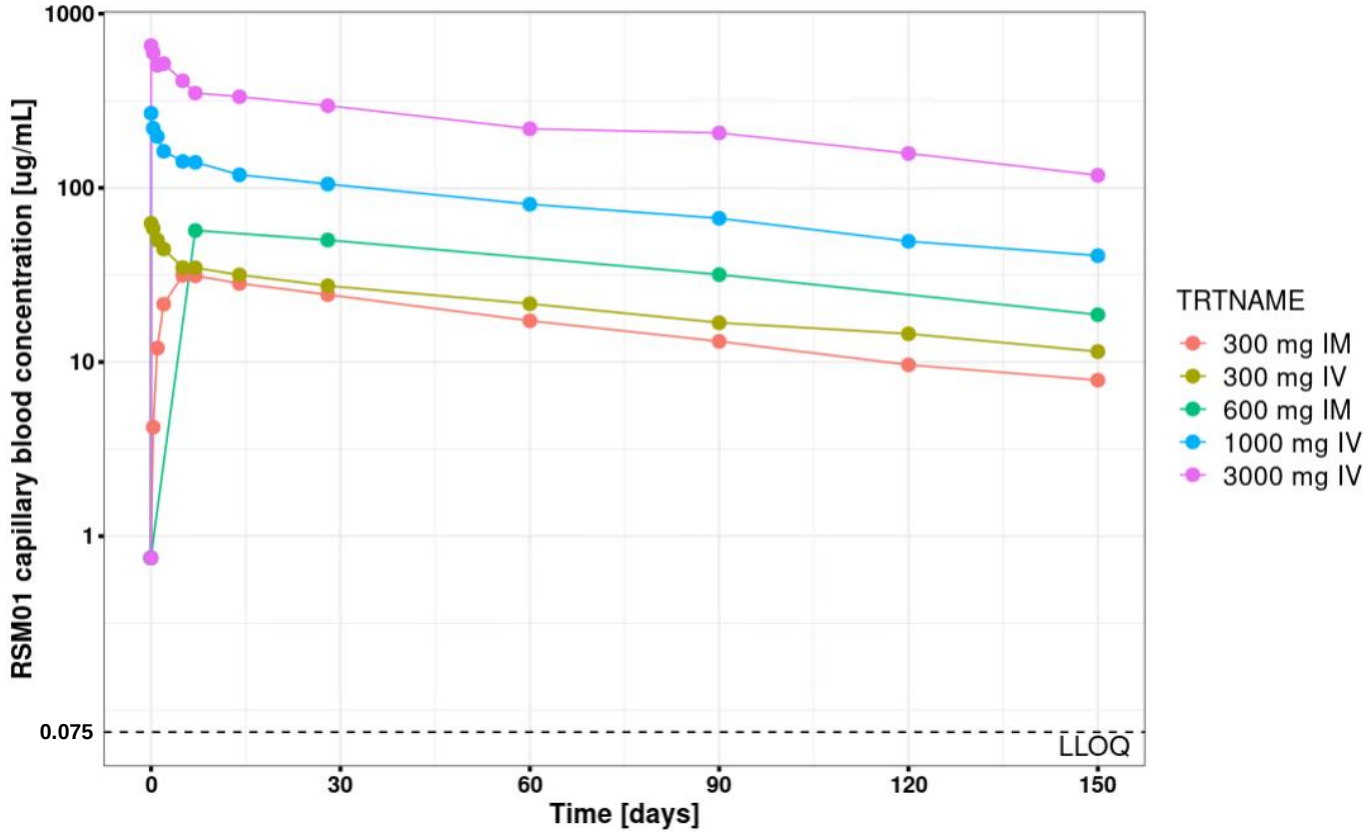
Gates MRI-RSM01-101: Mean RSM01 concentrations in serum and capillary blood

Similar mean concertation time profile in the serum and blood

Mean serum



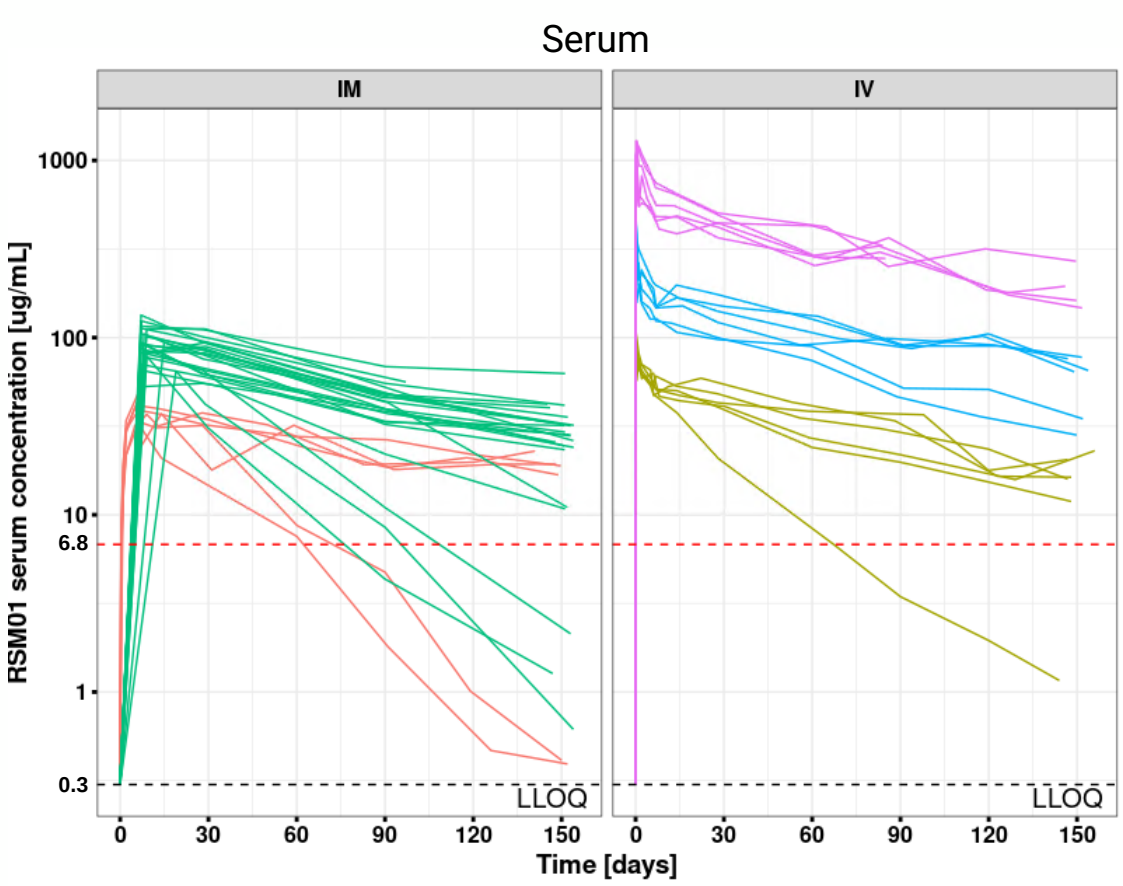
Mean blood

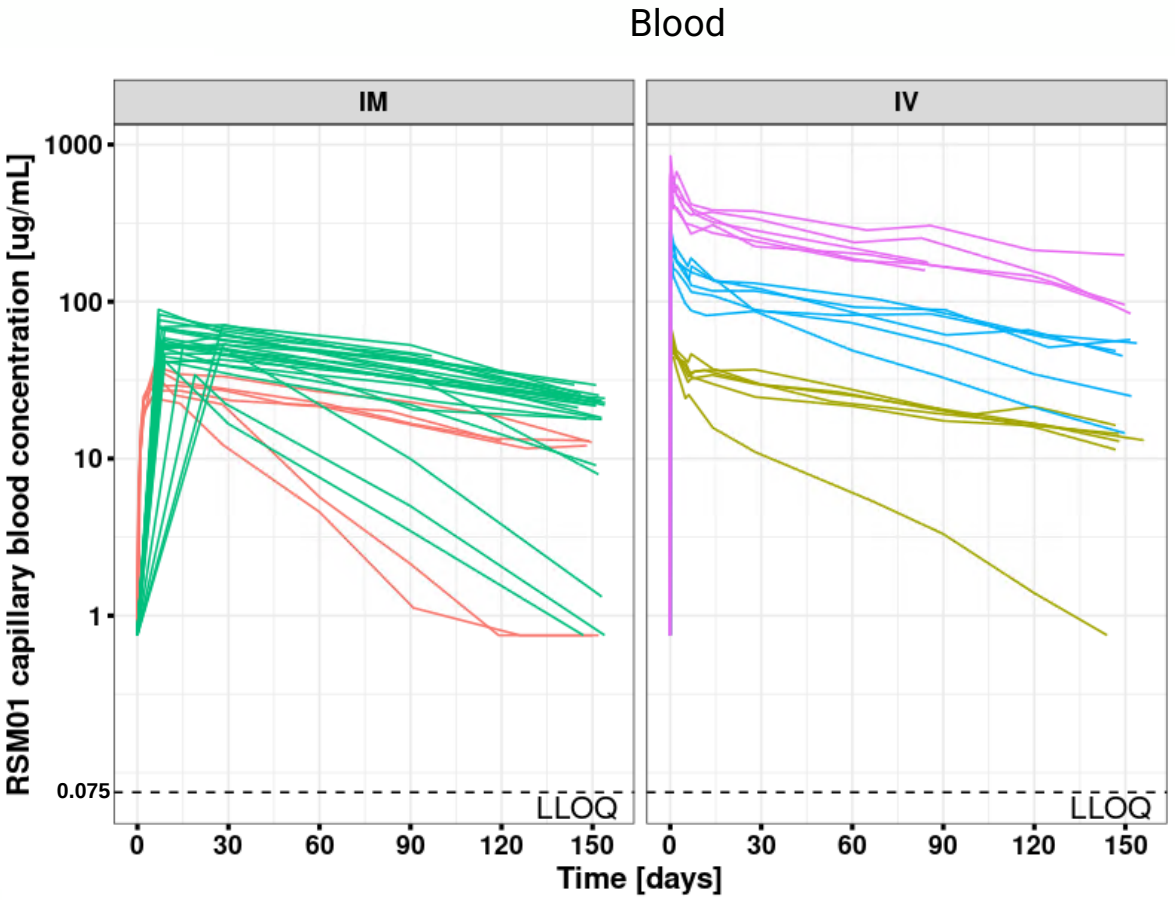


6.8 ug/mL is the efficacious concentration target. Estimated from cotton rat EC_{90} (RSM01 and nirsevimab) and nirsevimab clinical data

- PK is typical of a half-life prolonged mAb
- It is dose-linear across doses tested

Gates MRI-RSM01-101: Individual RSM01 concentrations are similar in serum and capillary blood

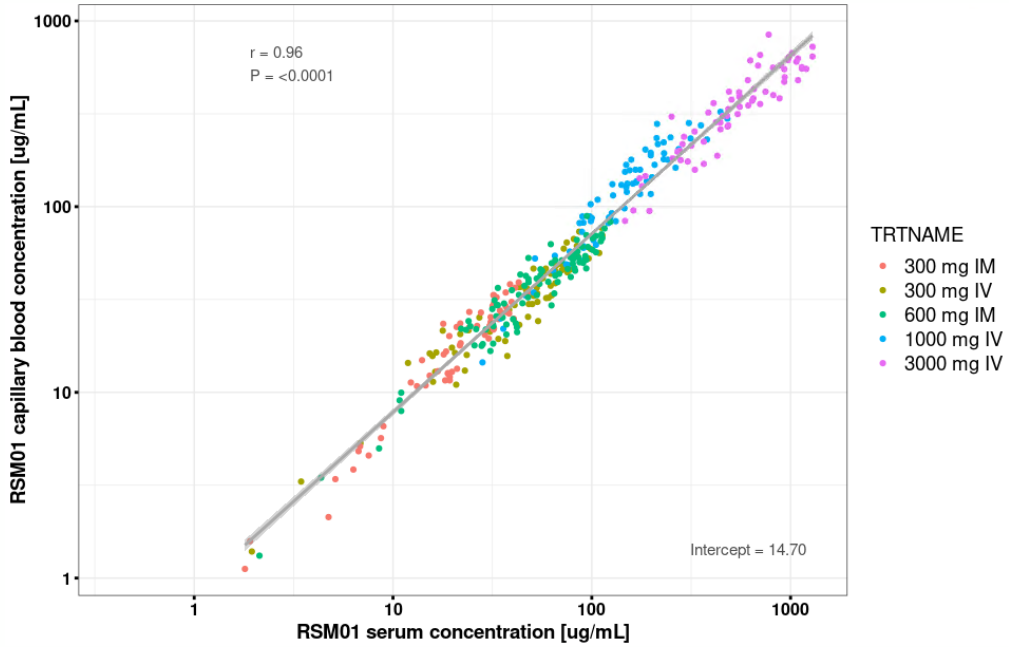




6.8 ug/mL is the efficacious concentration target. Estimated from cotton rat EC_{90} (RSM01 and nirsevimab) and nirsevimab clinical data

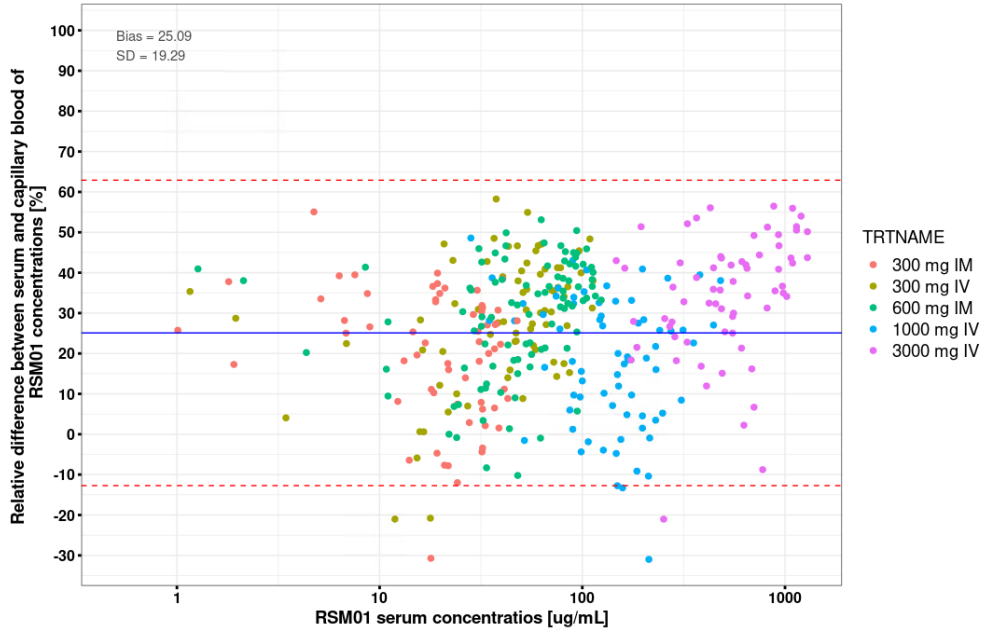
- There are few outliers with apparent higher elimination rates (consistent across two mediums)

Gates MRI-RSM01-101: There is a high correlation between serum and blood concentrations



r = correlation coefficient, P = p-value, Intercept = Intercept of the regression line

- All subjects show high correlations between the blood and plasma
- Generally, no discernable pattern emerges even when controlling for sex, race, or ethnicity



*Bias (mean of (Serum - Blood)/Serum*100%) as a solid blue line and the lower and upper limits of agreement (LOA) as dashed red lines*

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Population PK analysis demonstrated that the PK in capillary blood from VAMS and serum samples are comparable

- 2 compartment models with zero-order absorption (for IM) and first-order elimination for both serum and blood data described the data well
- As expected, due to mAb partition to serum, clearance and volume parameters were higher in the blood (by approximately 40%)
- However, a similar half-life was estimated in the blood and serum
- Bioavailability and the rate of absorption are not impacted by the matrix

Parameter [Unites]	Serum	Blood
CL (L/Day)	0.0477	0.0665
V (L)	3.21	4.4
Q (L/Day)	0.688	1.226
Vp (L)	2.18	3.16
D1 (Day)	3.86	4.03
Bioavailability (%)	82.3	81.1
Distribution $t_{1/2}$ (days)	1.29	1.02
Terminal* $t_{1/2}$ (Days)	79.1	79.6

* Terminal half-life is a close approximation of the beta half-life

Conclusions

- A patient-centric sampling strategy using dried blood collected on VAMS technology was successfully implemented for RSM01 in a first-in-human trial with adult participants
- The PK results in capillary blood from VAMS and serum samples were comparable with a high correlation coefficient
- This approach is valuable in advancing global clinical drug development and will be used in future pediatric RSM01 trials in infants

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