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

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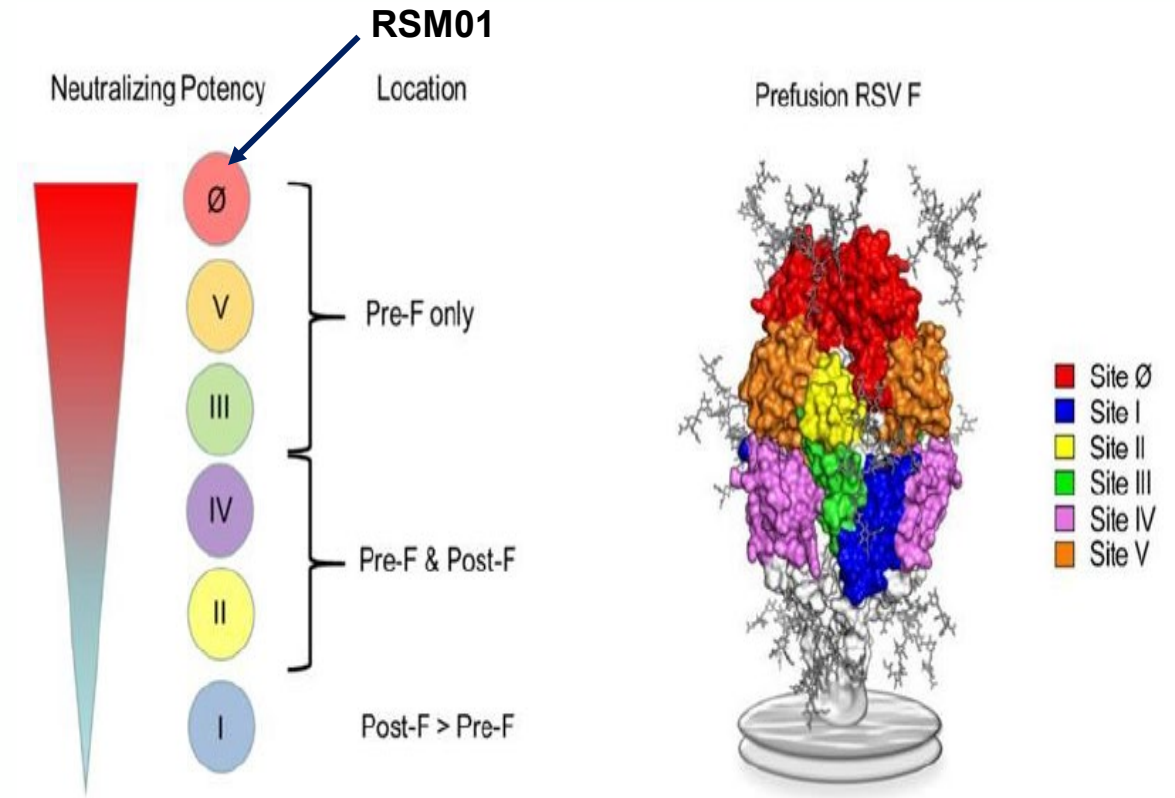
Respiratory Syncytial Virus (RSV) is a major global health concern, primarily affecting young children

- 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

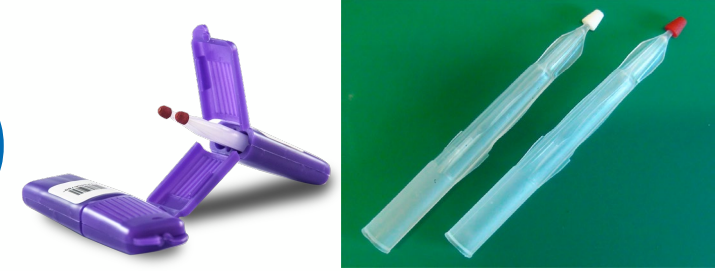


Hemapen



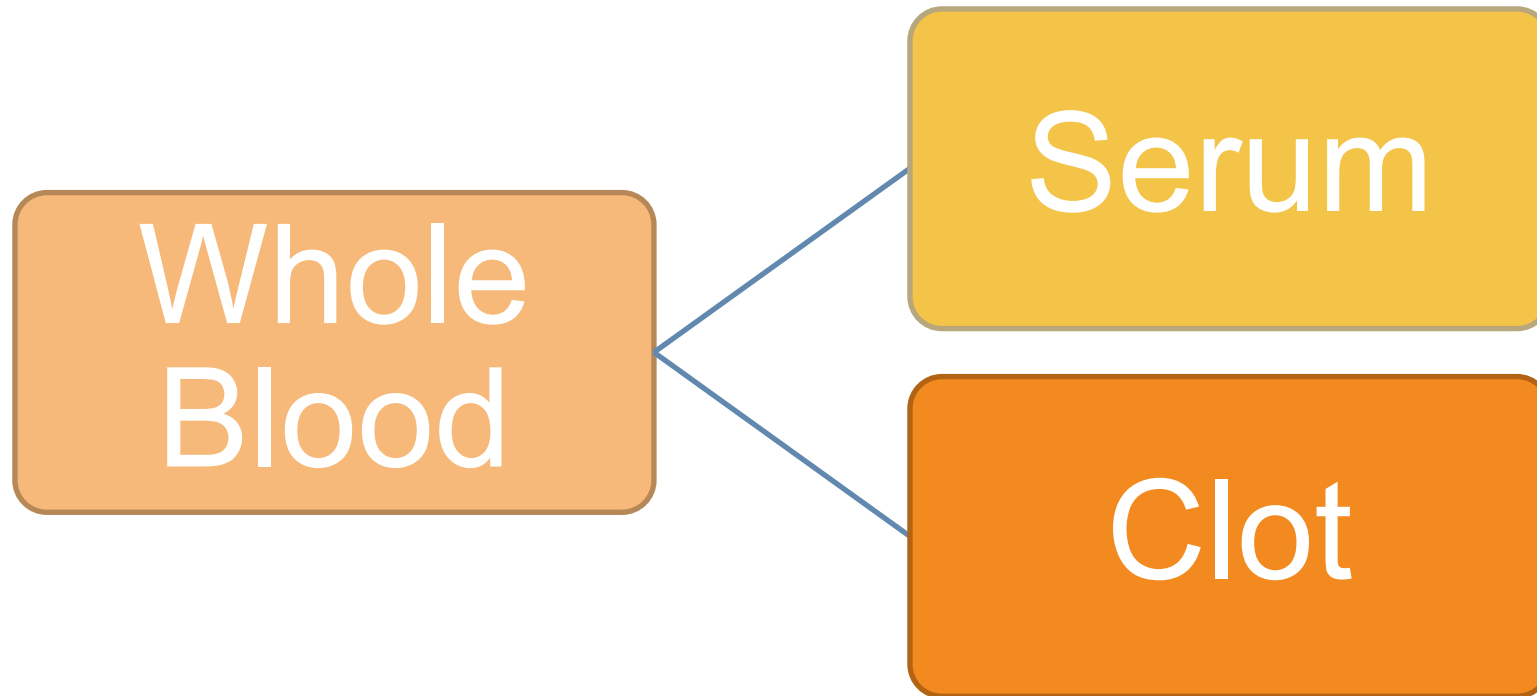
Mitra

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 μ L)
 - / 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

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 RSM01 in 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

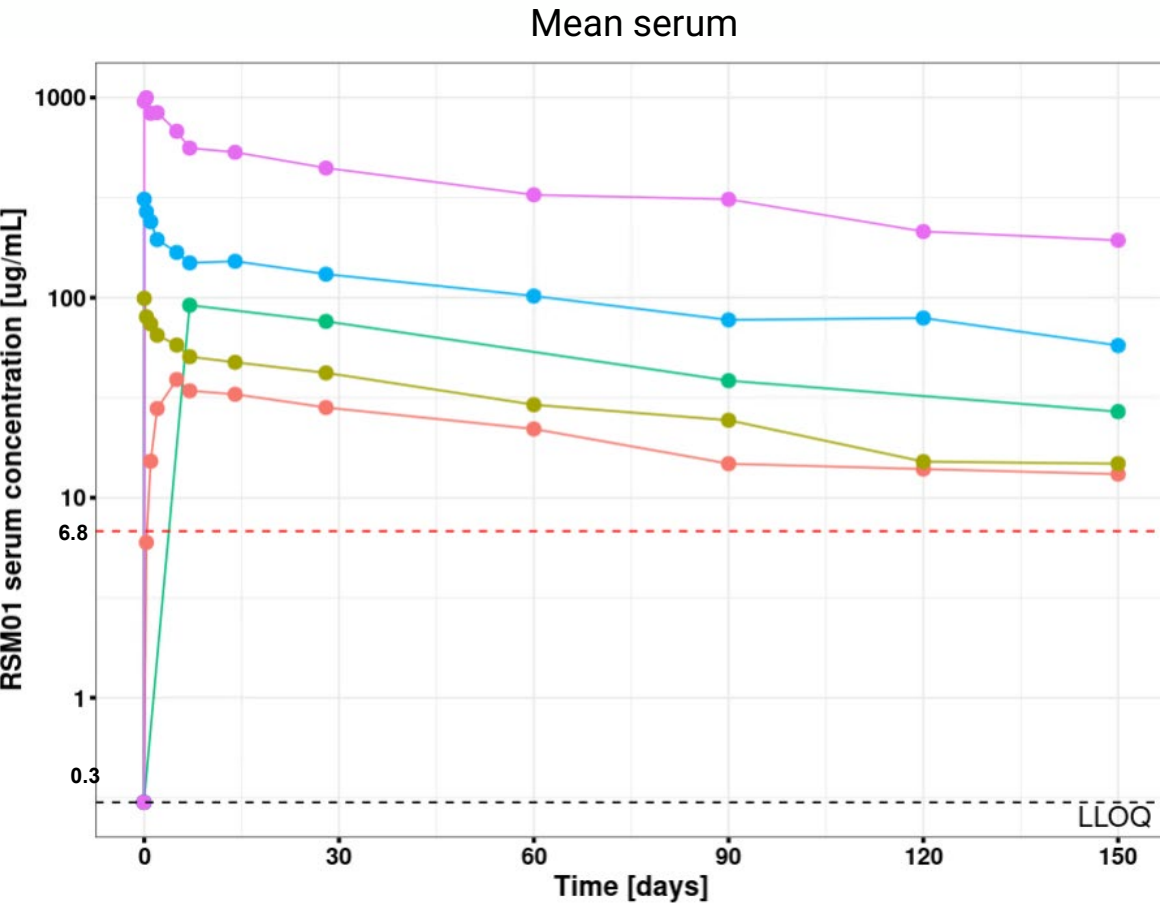
600 mg IM

RSM01, n = 24;

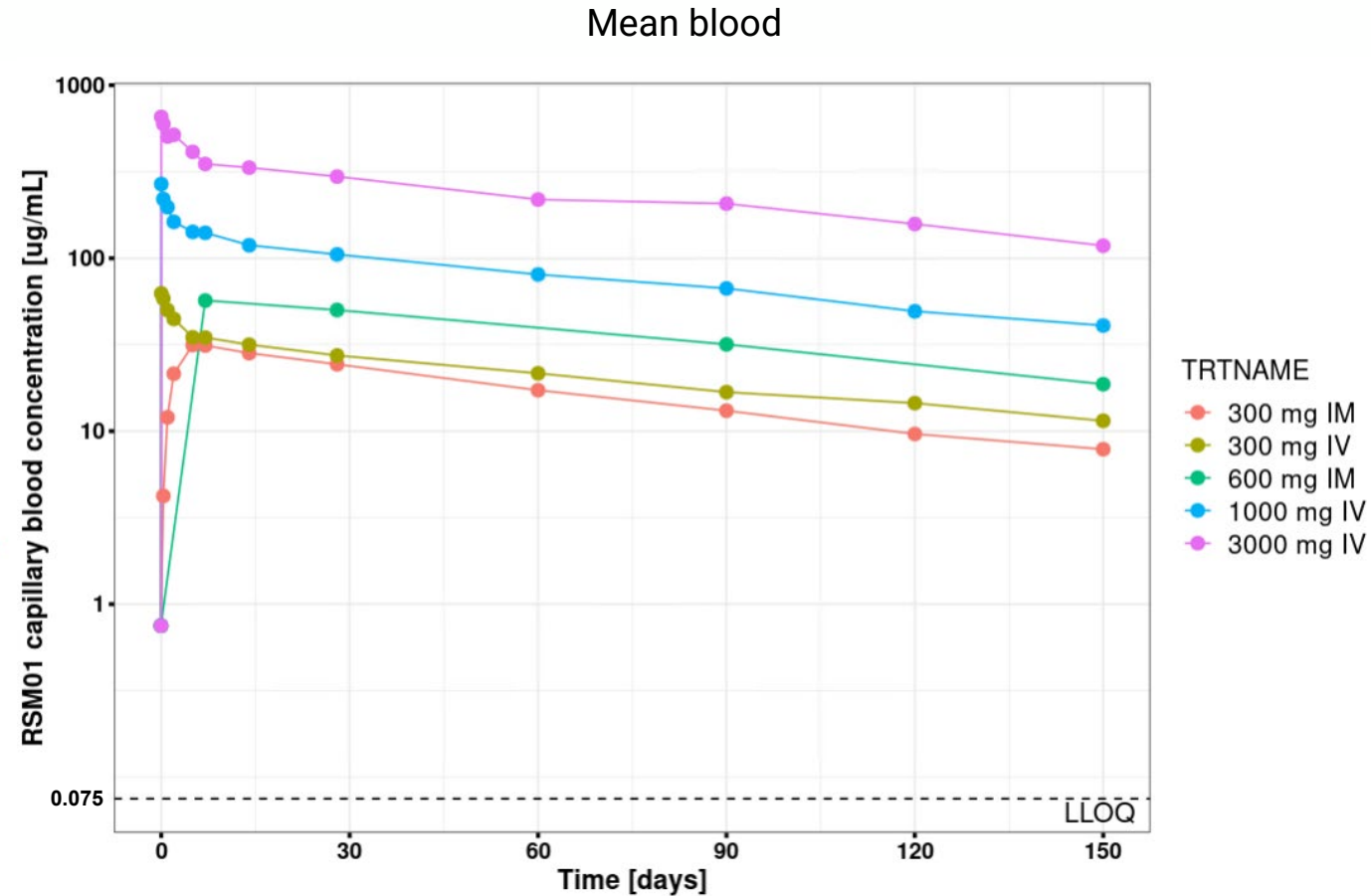
PBO, n = 4

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

Similar mean concentration time profile in the serum and blood

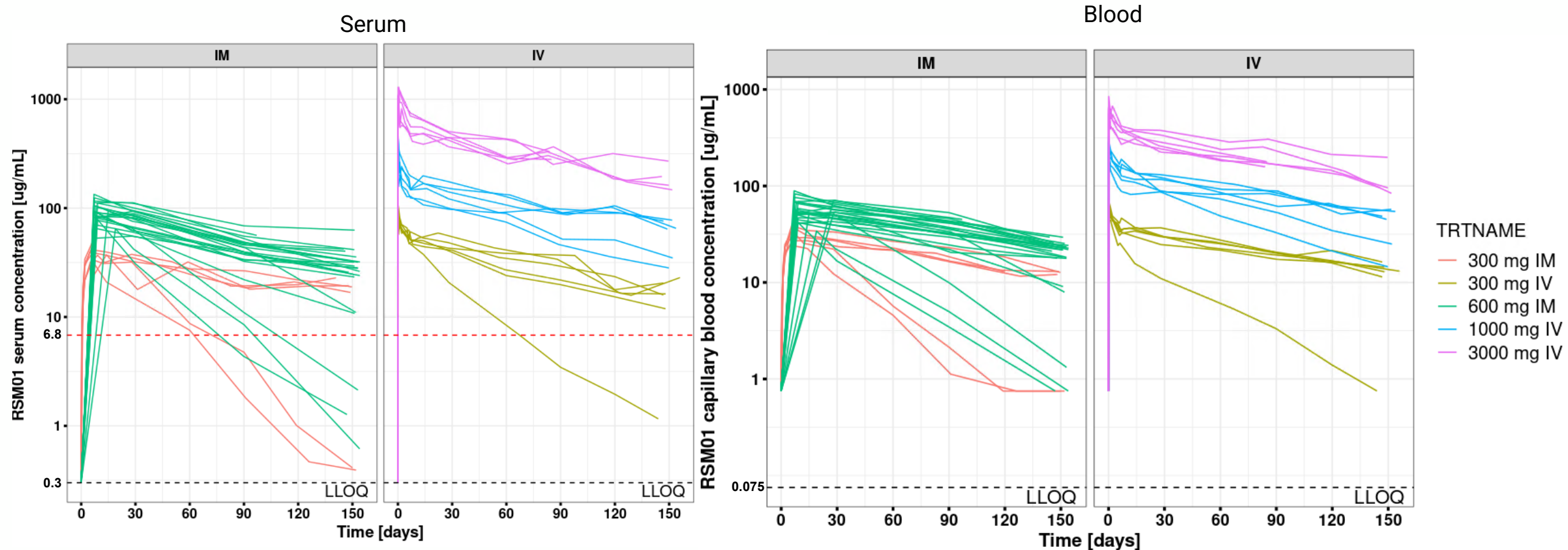


6.8 ug/mL is the efficacious concentration target. Estimated from cotton rat EC_{90} (RSM01 and nirsevimab) and nirsevimab clinical data



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

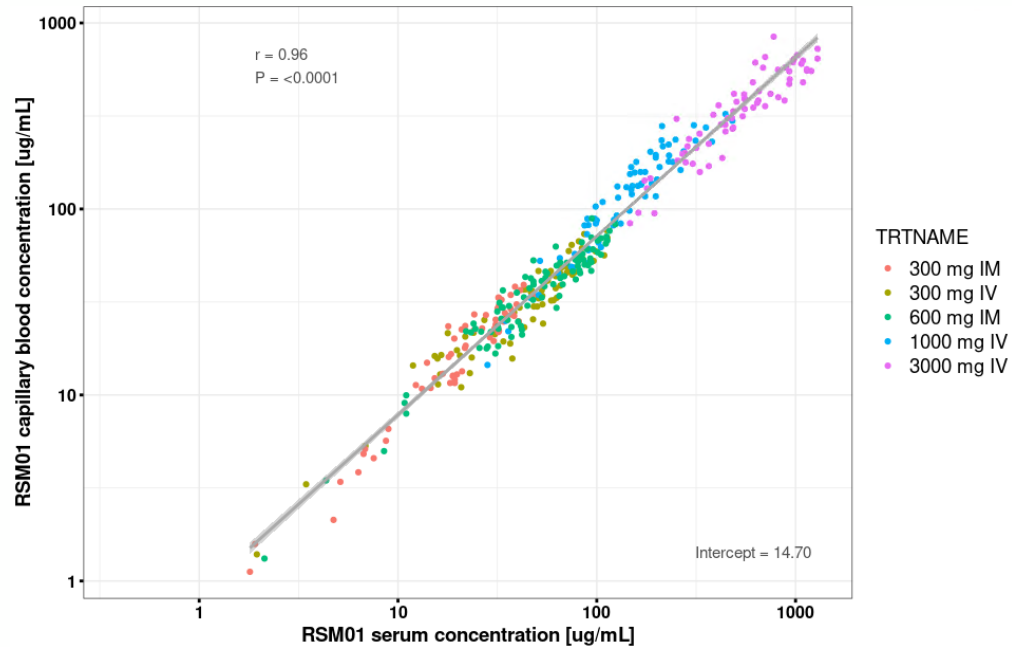
Gates MRI-RSM01-101: Individual RSM01 concentrations are similar in serum and capillary blood



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

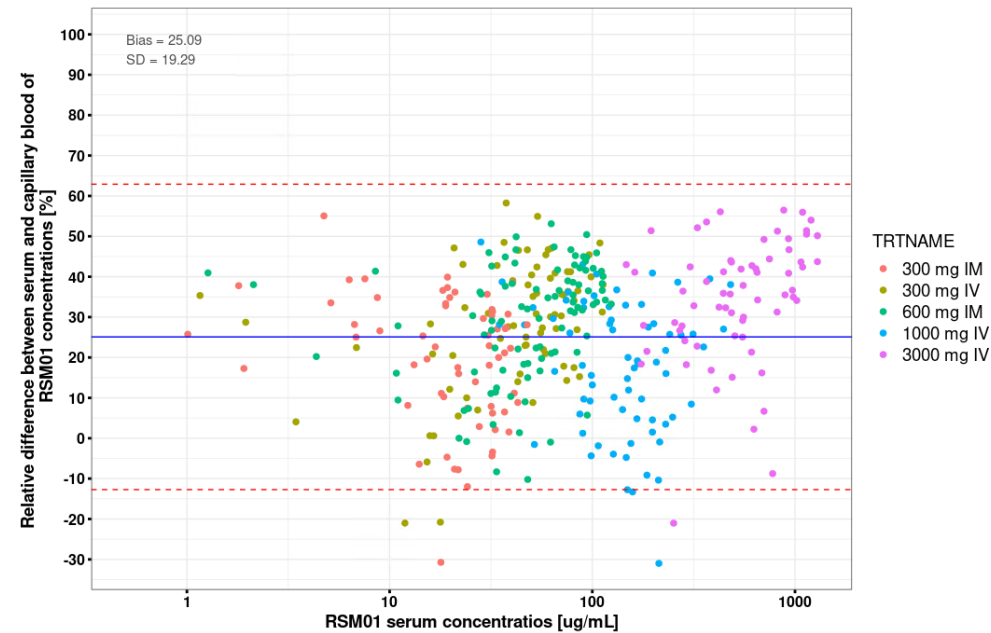
- There are few outliers with apparent higher elimination rates (consistent across two mediums)

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 $(\text{Serum} - \text{Blood})/\text{Serum} \times 100\%$) as a solid blue line and the lower and upper limits of agreement (LOA) as dashed red lines

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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