Bill & Melinda Gates Medical Research Institute

Gates MRI-RSM01-101

A Phase 1 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of RSM01, a Monoclonal Antibody Targeting Respiratory Syncytial Virus, in Healthy Adults

7 Sep 2022

Final Statistical Analysis Plan

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List of Abbreviations

ADA	Anti-drug antibody
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the (time) curve (e.g., capillary blood-concentration time curve)
BLQ	Below limit of quantification
C_{D91}	Day 91 capillary blood concentration of RSM01
C_{D151}	Day 151 capillary blood concentration of RSM01
C_{max}	Maximum capillary blood concentration of RSM01
C_{min}	Minimum capillary blood concentration of RSM01
CL	Total body clearance
CL/F	Apparent total body clearance
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
EC90	90% maximal effective concentration
F	Bioavailability
Gates MRI	Bill & Melinda Gates Medical Research Institute
GGT	Gamma glutamyl transferase
HIV	Human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IV	Intravenous
IXRS	Interactive voice/web response system
mAb	Monoclonal antibody
Mg	Milligram
mL	Milliliter
NA	Not applicable
NCA	Noncompartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
RSM01	Monoclonal antibody targeting Respiratory Syncytial Virus
RSV	Respiratory Syncytial Virus
Rsq	R squared
SAE	Serious adverse event
SAP	Statistical analysis plan
SRT	Safety Review Team
$t_{1/2}$	Apparent terminal half-life
T_{max}	Time to maximum capillary blood-concentration of RSM01

VAMS	Volumetric absorptive microsampling
Vz	Volume of distribution
Vz/F	Apparent volume of distribution
λ_z	Elimination rate constant

1. Introduction

The high and continued burden of Respiratory Syncytial Virus (RSV) infection, especially among infants and young children, underscores the need for safe and effective prevention against RSV disease that is affordable in low- and middle-income countries (LMICs).

This Phase 1 study will evaluate the safety, tolerability, and pharmacokinetics in adults of an RSV monoclonal antibody (mAb) candidate engineered to be highly neutralizing and long acting, and to determine an appropriate dose with acceptable safety profile in adults, prior to administration to infants in a future clinical study. Adult participants will receive either intravenous (IV) or intramuscular (IM) doses of RSM01, which will enable the assessment of the safety profiles together with estimation of the human bioavailability following IM injection, which is the intended route of administration in infants.

The purpose of this statistical analysis plan (SAP) is to define the planned analyses of the study data to address the study objectives. This SAP is written based on protocol Gates MRI-RSM01-101, Version 4.0, dated 21 Jan 2022.

2. Objectives and Endpoints

2.1 Primary Objectives and Endpoints

Primary objective	**Endpoint description**
• To characterize the safety and tolerability of a single dose of RSM01	• Unsolicited adverse events (AEs) through Day 151 • All serious adverse events (SAEs) and AE of special interest (AESIs) through Day 151 • Solicited systemic AEs for 7 days after dose administration (applies to both IV and IM doses) • Solicited local AEs for injection site reactions for 7 days after dose administration (only applies to IM doses)

2.2 Secondary Objectives and Endpoints

Secondary objectives	**Endpoint description**
• To characterize safety laboratory parameters following RSM01 administration	• Safety laboratory parameters through Day 151
• To characterize the pharmacokinetics (PK) following RSM01 administration	PK parameters including: • Area under the capillary blood-concentration time curve from zero to infinity ($AUC_{0\text{-}inf)}$ • Day 91 concentration and area under the capillary blood-concentration time curve (C_{D91} and $AUC_{0\text{-}D91}$) • Day 151 concentration and area under the capillary blood-concentration time curve (C_{D151} and $AUC_{0\text{-}D151}$) • Maximum capillary blood-concentration (C_{max} following IM administration and C_0 following IV administration) • Minimum concentration (C_{min}) • Time to maximum capillary blood-concentration (T_{max}) and apparent terminal half-life ($t_{1/2}$) • Systemic clearance (CL for IV or CL/F for IM) • Volume of distribution of RSM01 (V_z for IV or V_z/F for IM) through Day 151
• To characterize the formation of anti-drug antibodies (ADAs) following RSM01 administration	• Incidence of ADAs to RSM01 through Day 151

2.3 Exploratory Objectives and Endpoints

Exploratory objective	Endpoint description
• To characterize RSV neutralizing antibody activity following RSM01 administration	• Capillary blood RSV neutralizing antibody levels through Day 151

3. Study Design

This is a First-in-Human (FiH) trial of RSM01, administered to adults. It is a randomized, double-blind, placebo-controlled study of RSM01.

Candidates will be screened to enroll and randomize approximately 56 eligible participants. Assuming all cohorts will be open to enrollment, approximately 48 participants will be exposed to RSM01, and approximately 8 participants will be exposed to placebo. Within each cohort, there will be no replacement participants.

If a participant fails to meet eligibility criteria upon initial screening, a one-time only rescreening for eligibility may be performed.

The study will be conducted in 2 parts: A Dose Escalation Phase (N=28) with 4 dosing cohorts, followed by an Expansion Phase (N=28) with a single cohort.

The first participant in each Dose Escalation Phase cohort will not be randomized and will receive the RSM01 dose level appropriate to the assigned cohort to serve as a sentinel exposure participant. The remaining 6 participants in each of Cohorts 1, 2, 3, and 4 will be randomized 5:1 to receive either RSM01 or Placebo. The overall ratio of RSM01 to Placebo will be 6:1 in each cohort.

The Dose Escalation Phase will have 2 escalation steps.

- Cohort 1: 7 participants to receive RSM01 300mg IV (n=6 total including sentinel participant) or placebo (n=1)

First escalation step: from Cohort 1 to Cohorts 2 and 3, in parallel. Participants in Cohort 1 are to be randomized in a 1:1 manner to either Cohort 2 or Cohort 3.

- Cohort 2: 7 participants to receive RSM01 300mg IM (n=6 total including sentinel participant) or placebo (n=1)
- Cohort 3: 7 participants to receive RSM01 1000mg IV (n=6 total including sentinel participant) or placebo (n=1)

Second escalation step: from Cohorts 2 and 3 to Cohort 4

- Cohort 4: 7 participants to receive RSM01 3000mg IV (n=6 total including sentinel participant) or placebo (n=1)

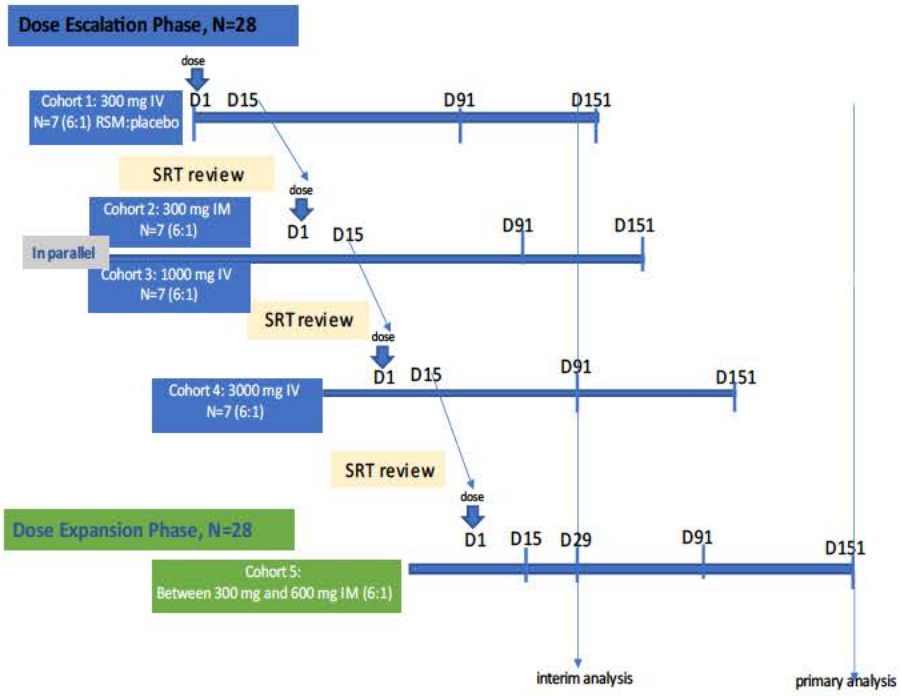
Each dose escalation step and enrollment into the Dose Expansion Phase will proceed after the prior cohort has completed Day 15, and the safety review team (SRT) has reviewed the data and determined that there are no events necessitating a pause.

The dose expansion phase will have one cohort:

- Cohort 5: participants to receive RSM01 IM (n=24) at a dose to be determined (TBD mg IM) or placebo (n=4).

The tentatively determined dose to be evaluated in the Expansion Phase Cohort is ≥300 mg to ≤600 mg IM. Final selection of the dose administered to Cohort 5 will be made by the sponsor and informed by available RSM01 PK data from the Dose Escalation Phase.

Figure 1: Schema of Study Design and Dosing Procedures



Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. Any one of the following will prompt a study pause:

- death in any participant in whom the event causing death is judged to be related to the study drug by the investigator.
- any occurrence in any participant of a SAE judged to be related by the investigator.
- any occurrence in any participant of an AESI (anaphylaxis, hypersensitivity reaction, and/or infusion reaction resulting in permanent discontinuation of study drug infusion during IV administration).
- any occurrence of Grade 3 or higher severity assessed to be related to the study drug by

the investigator.

- any occurrence of a clinically significant Grade 3 or higher laboratory abnormality assessed to be related to the study drug by the investigator.

If any of the pausing criteria are met, enrollment/patient accrual as well as dosing of enrolled participants will be suspended pending IDMC's review of all available safety data.

After screening, there will be a total of 11 visits over 151 days for the Dose Escalation Phase and a total of 5 visits over 151 days for the Dose Expansion Phase. An interim analysis will occur after all participants in the dose escalation cohorts (Cohorts 1 to 4) have reached Day 91. The primary analysis will occur after all participants in all 5 cohorts complete Day 151.

A more detailed Schedule of assessments can be found in Section 15.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of participants, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables, listings, and figures will be presented by cohort and treatment group. The treatment groups below will be used for presentations:

- RSM01 – 300 mg IV (Cohort 1)
- RSM01 – 300 mg IM (Cohort 2)
- RSM01 – 1000 mg IV (Cohort 3)
- RSM01 – 3000 mg IV (Cohort 4)
- RSM01 – TBD mg IM (Cohort 5)
- Total RSM01 treatment group
- Placebo IV (Cohorts 1, 3, 4)
- Placebo IM (Cohorts 2, 5)
- Total Placebo treatment group

All data listings will be sorted by cohort, treatment group, and participant number.

Study days are calculated with respect to study intervention administration date as below:

- If the assessment/observation date is on or after study intervention administration date, then Study Day = Assessment/Observation Date – Study Intervention Administration Date + 1.
- Otherwise, Study Day = Assessment/Observation Date – Study Intervention Administration Date.

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before study intervention administration, unless otherwise specified. If a patient

was rescreened, data from the rescreening period and not the original screening period will be used in the analyses as applicable.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

For ADA-positive participants, the date of the first positive ADA result will be considered as the start date of ADA response.

Time to post-baseline ADA detection (weeks) will be calculated as:

(Date of first positive ADA assessment – Study Intervention Administration Date + 1) / 7

If the first positive ADA is prior to the start of treatment, the formula is revised to:

(Date of first positive ADA assessment – Study Intervention Administration Date) / 7

Duration of ADA immunogenicity response (weeks) is defined as:

(Date of last positive ADA assessment – date of first positive ADA assessment + 1) / 7

For participants with pre-existing positive, duration will be calculated from administration date of RSM01 rather than from date of first positive assessment.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1. Handling of Missing Data

4.1.1 Missing or Partial Dates for Adverse Events

Missing or partial AE start dates will be imputed for the purpose of determining whether the AEs are treatment emergent. Data handling rules for missing or partial start/stop date for AEs are detailed in the table below. The missing or partial dates will be displayed in the data listings as reported on the electronic case report form (eCRF) rather the imputed dates.

Date	Situation	Imputation Rule
AE Start Date	Only month and year are known, and month is prior to first dose date	Use the first day of the month
	Only month and year are known, and month is the same as first dose date	Use the first dose date
	Only month and year are known, and month is after first dose date	Use the first day of the month
	Only year is known, and year is after first dose date	Use Jan 1 of that year
AE End Date	Only month and year are known, and month is prior to last dose date	Use the last day of the month
	Only month and year are known, and month is the same as last dose date	Use the last dose date
	Only month and year are known, and	Use the first day of the month

	month is after last dose date	
	Only year is known, and year is before last dose date	Use Dec 31 of that year
	The estimated stop date is before a complete or imputed AE start date	Use the last day of the month of the AE start date
AE = adverse event Note: Imputation of end date must be later than start date.		

4.1.2 Missing Incomplete Dates for Prior or Concomitant Medications

Missing or partial medication start or stop dates will be imputed for the purpose of determining whether the medication is taken concomitantly. Data handling rules for missing or partial start/stop date medications are detailed in the table below. The missing or partial dates will be displayed in the data listings as reported on the eCRF rather the imputed dates.

Imputation rules for missing or partial dates (D=day, M=month, Y=year, T=time)			
Parameter	**Missing**	**Additional conditions**	**Imputation Rule**
Start date	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as M and Y of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D and Y	None--date completely missing	Date of first dose of study drug
Stop date	D only	M and Y same as M and Y of end of study	Date of end of study
		M and/or Y not same as M and Y of end of study	Last day of month
	M and D	Y same as Y of end of study	Date of last dose of study drug
		Y not same as Y of end of study	Use Dec 31 of Y
	M, D and Y	Medications that are not marked as ongoing - date completely missing	Date of end of study

4.2. Sample Size

This is an exploratory trial to characterize safety, tolerability, and pharmacokinetics of single dose of RSM01 mAb administered by either IV or IM routes. The trial is designed to be descriptive and is not based on evaluation of a formal null hypotheses. Therefore, this study is not powered to detect any differences in potential safety observations between treatment groups. Data from approximately 56 participants will be available for analysis: 28 participants in the Dose Escalation Phase Cohorts and 28 participants in the Dose Expansion Phase Cohort.

Assuming that all cohorts are allowed to undergo treatment, approximately 48 participants will be exposed to RSM01, and approximately 8 participants will receive Placebo.

With N=6 participants (per RSM01 arm in Dose Escalation Phase cohorts), there is approximately 80% (90%) power to observe at least one AE if the true AE rate is 23.53% (31.87%). With N=24 participants (across all active doses of RSM01 in the Dose Escalation Phase cohorts or the Dose Expansion Phase Cohort), there is approximately 80% (90%) power to observe at least one AE if the true AE rate is 6.49% (9.15%). Across all active doses of RSM01 (N=48), there is approximately 80% (90%) power to observe at least one AE if the true AE rate is 3.3% (4.68%).

4.3. Randomization and Blinding

The first participant in each Dose Escalation Phase cohort will not be randomized and will receive RSM01 dose level appropriate to the assigned cohort in a single-blinded fashion: participants will be blinded to treatment, but site will not be blinded to treatment. Subsequent participants in the cohort will be double-blinded: participants and site personnel, except for the study pharmacist, will be blinded to treatment. The study pharmacist will know assignment to provide doses of RSM01 and Placebo to the clinic that are appropriately masked to the blinded treating nurse/physician.

The remaining 6 participants in each cohort (Cohorts 1, 2, 3 and 4) will be randomized 5:1 to receive either RSM01 or placebo. Cohorts 2 and 3 will be enrolled in parallel using 1:1 randomization. The overall ratio of RSM01 to placebo will be 6:1 in each cohort. The Expansion Phase cohort (Cohort 5) will be randomized 6:1 to receive either RSM01 IM (N=24) or placebo (N=4).

Randomization in each cohort will be based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IXRS).

The randomization schedule will be prepared by a statistician who will not be involved in the analysis of the study in order to maintain the blind of the study team.

With the exception of the first sentinel participant in each of the Dose Escalation Phase cohorts who will each receive the respective dose of RSM01, the study is double-blind: participants and all study personnel will be blinded to the randomization.

An interim analysis will be performed after availability of Cohort 2, Cohort 3, and Cohort 4 Day 30 data (see Section 11). Firewalled roles will be involved in the interim analysis to create unblinded datasets and perform analyses. The investigator will remain blinded. The sponsor will review blinded (pooled) safety data by cohort and unblinded aggregated PK data by treatment group (RSM01 vs. placebo) within and across cohorts. The sponsor will be blinded at the participant level throughout the study. For expedited safety reporting to regulatory authorities,

pharmacovigilance unblinding will be performed as required. Information regarding unblinding for the interim analysis is contained in a separate unblinding plan.

The IXRS will be programmed with blind-breaking instructions. In addition, instructions on emergency unblinding in case of system outage will be provided.

4.4. Analysis Populations

Population	Description
Enrolled population	All participants enrolled for screening. Participants randomly assigned to study treatment will be classified according to the intervention they were randomized to receive.
Safety Population	All participants who received the study treatment. Participants will be analyzed according to the intervention they received.
Per protocol (PP) Population	All participants who received study treatment and did not have a significant protocol deviation. Participants will be analyzed according to the intervention they received.
PK Population	All participants who received RSM01 who have a baseline and at least one post-baseline PK result. Participants will be analyzed according to the intervention they received.
Immunogenicity Population	All participants who received the study treatment and have at least one valid post-baseline ADA sample. Participants with no baseline ADA assessment are assumed to be negative at baseline. Participants will be analyzed according to the intervention they received.

5. Participant Disposition

5.1 Disposition

The following will be summarized for the enrolled population, by treatment group and overall for all participants:

- The number of participants who were randomized in each cohort
- The number of participants who received each treatment
- The number of participants who completed the study
- The number of participants who did not complete the study (both overall and according to reasons for study withdrawal)

- The number of participants who were unblinded by the site
- The number of participants in each analysis population
- The number of participants who screen failed (both overall and according to reasons for screen failure)

Participant disposition and screen failure data will be presented in data listings.

5.2 Protocol Deviations

Significant protocol deviations will be summarized by treatment group. All protocol deviations will be presented in a data listing. Protocol deviations will be maintained in an Excel spreadsheet, which will include the deviation description, date of deviation, deviation category, and significance (significant/not significant). The protocol deviation spreadsheet will be finalized prior to database lock.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing.

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic and other baseline information collected at screening will be presented in a data listing. Descriptive statistics will be calculated for the following continuous demographic and other baseline characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)
- Pulse rate (beats/minute)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Temperature (C)
- Oxygen saturation (%)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity

The summaries will be presented by treatment group and overall for the safety population.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]) and summarized by treatment group. All medical history data will be presented in a data listing.

7. Treatments and Medications

7.1 Prior and Concomitant Medications

Medications that are discontinued prior to study intervention administration will be classified as prior medication. Medications for which dosing is begun on or after study intervention administration will be classified as concomitant. If a medication is begun before study intervention administration and is discontinued on or after study intervention administration, then the medication will be classified as both prior and concomitant.

All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (version to be delineated in the CSR) and presented in a data listing.

7.2 Study Treatment

The study drug administration as collected on eCRF will be presented in the data listings.

8. Pharmacokinetics

8.1. Pharmacokinetic Concentrations

Whole blood samples on VAMS and serum samples will be collected for measurement of RSM01 concentrations in capillary blood and venous serum as below:

Dose Escalation Phase:

- At Visit 1 (Day 1), PK blood draw will occur pre-dosing, within 5 minutes (± 1 minute) after end of infusion for IV dosing only, and at 8-hours (± 0.5 hours) post-dose for both IV and IM doses.
- Visit 2 (Day 2): 24-hours (± 1 hours)
- Visit 3 (Day 3): (± 0 day)
- Visit 4 (Day 6): (± 1 day)
- Visit 5 (Day 8): Days 8-10
- Visit 6 (Day 15): (± 3 days)
- Visit 7 (Day 29): Days 29-35
- Visit 8 (Day 61): (± 7 days)
- Visit 9 (Day 91): (± 7 days)
- Visit 10 (Day 121): (± 7 days)
- Visit 11 (Day 151): (± 7 days)
- Discontinuation visit

Dose Expansion Phase:

- At Visit 1 (Day 1): pre-dose

- Visit 2 (Day 8): Days 8-10
- Visit 3 (Day 29): Days 29-35
- Visit 4 (Day 91): (± 7 days)
- Visit 5 (Day 151): (± 7 days)
- Discontinuation visit

Individual capillary blood concentration of RSM01 and time deviation data for PK population will be presented in data listings. Capillary blood concentration data will be summarized by scheduled time point for the PP population using descriptive statistics (non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), median, minimum, maximum, Q1 and Q3. Capillary blood concentration data will also be summarized by ADA status using the PK population.

Descriptive statistics of capillary blood concentration of RSM01 data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PP PK concentration data:

- Mean, Min, Median, Max, Q1, Q3: 3 significant digits
- SD: 4 significant digits
- CV%: 1 decimal place

Concentrations of RSM01 that are below the lower limit of quantification (BLQ) before the first quantifiable concentration will be treated as zero for descriptive statistics. Below the limit of quantification values after the first quantifiable concentration will be set as missing and excluded for summary statistics.

Mean (±SD) capillary blood concentrations of RSM01 versus scheduled time profiles will be plotted by treatment on both linear and semi-logarithmic scales for PK population. Individual capillary blood concentrations versus actual time profiles will be plotted on both linear and semi-logarithmic scales for the PP population. The ADA status for each subject will be displayed on the individual profiles and for ADA positive participants, the titer results will be plotted on the secondary Y-axis.

The same analyses will be performed for venous serum (exploratory objective).

8.2. Pharmacokinetic Parameters

Individual capillary blood concentration of RSM01 versus actual time data will be used to estimate the PK parameters of RSM01 by standard noncompartmental methods using WinNonlin (Phoenix) version 8.0 or higher. For the calculation of PK parameters, BLQ values before the first quantifiable concentration of RSM01 will be treated as zero. Below the limit of quantification values after the first quantifiable concentration will be set as missing. Missing concentrations will be treated as missing. If consecutive BLQ concentrations of RSM01 are

followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

The following PK parameters for capillary blood RSM01 will be calculated for dose escalation cohorts and dose expansion cohort, if data permit.

Parameter	**Description**
C_{max}	Maximum observed capillary blood concentration of RSM01
C_{min}	Minimum observed capillary blood concentration of RSM01
C_{D91}	Day 91 capillary blood concentration of RSM01
C_{D151}	Day 151 capillary blood concentration of RSM01
T_{max}	Time to reach maximum observed capillary blood concentration of RSM01
$AUC_{0\text{-}inf}$	Area under the capillary blood concentration curve for RSM01 from time 0 to the infinity, calculated using the linear trapezoidal linear interpolation method
$AUC_{0\text{-}D91}$	Area under the capillary blood concentration curve for RSM01 from time 0 to Day 91, calculated using the linear trapezoidal linear interpolation method
$AUC_{0\text{-}D151}$	Area under the capillary blood concentration curve for RSM01 from time 0 to Day 151, calculated using the linear trapezoidal linear interpolation method
CL	Total body clearance (for IV); calculated as Dose/$AUC_{0\text{-}inf}$
CL/F	Apparent total body clearance (for IM); calculated as Dose/$AUC_{0\text{-}inf}$
V_z	Volume of distribution (for IV); calculated as Dose/($AUC_{0\text{-}inf}$ x $\lambda_{z)}$
V_z/F	Apparent volume of distribution (for IM); calculated as Dose/($AUC_{0\text{-}inf}$ x $\lambda_{z)}$
$t_{1/2}$	Apparent terminal half-life; calculated as $0.693/\lambda_z$

The following PK parameters will be calculated for diagnostic purposes and listed, but they will not be summarized.

Parameter	Description
λ_z	Elimination rate constant, calculated by linear regression of the terminal portion of the natural log capillary blood concentration versus time curve. Visual assessment may be used to identify the terminal linear phase of the natural log capillary blood concentration versus time profile. A minimum of 3 data points (excluding C_{max} for IM) will be used for calculation. The parameter λ_z will not be calculated if the terminal phase of the natural log capillary blood concentration versus time profile does not exhibit a linear decline phase or if the Rsq < 0.8
λ_z lower	Lower limit of time included in the calculation of λ_z
λ_z upper	Upper limit of time included in the calculation of λ_z
λ_z N	Number of data points used in the calculation of λ_z
Rsq	Regression coefficient for calculation of λ_z.

Additional PK parameters may be calculated. Individual capillary blood RSM01 PK parameters will be presented in the data listings for the PP population. The capillary blood RSM01 PK parameters will be summarized using the PP population by treatment with the following descriptive statistics: N, n, mean, SD, CV, median, minimum, maximum, geometric mean, and geometric percent CV.

Capillary blood PK parameters for RSM01 will be displayed to 3 significant figures in all data listings and summary tables, with exception of time variables (T_{max}, λ_z lower, and λz upper) which will be displayed to 2 decimal places. λ_z which will be displayed to 4 decimal places.

Scatter plots of capillary blood RSM01 PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}D91}$, $AUC_{0\text{-}D151}$, and C_{max}) vs. IV dose will be plotted with an equation and R^2 value.

The same analyses will be performed for venous serum (exploratory objective).

8.3. Statistical analysis

Dose proportionality for capillary blood RSM01 PK parameters will be tested using the power regression model for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}D91}$, $AUC_{0\text{-}D151}$, and C_{max} and, defined as:

$$\ln [\text{PK parameter}] = \beta 0 + \beta 1 \ln [\text{Dose}]$$

where the PK parameter is an $AUC_{0\text{-}inf}$, $AUC_{0\text{-}D91}$, $AUC_{0\text{-}D151}$, and C_{max}. The null hypothesis being tested is that the AUC and C_{max} values are dose proportional, or slope (β1) = 1. Dose-proportionality will be concluded if the 90% CI of the slope β1 lies entirely within [1+ln(0.5)/ln(r), 1+ln(2.0)/ln(r)], where r is a ratio that describes the dose range and is defined as the ratio of highest dose/lowest dose.

Bioavailability of RSM01 following IM injection will be calculated using the ratio of geometric mean of $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}D151}$ capillary blood RSM01 PK parameters for the comparison of IM versus IV dose. Log-transformed $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}D151}$ estimates will be analyzed using an analysis of variance (ANOVA) model with treatment group as a factor. The parameter estimates results will be exponentiated and the ratio of geometric means and 90% CIs will be presented.

The proportion of participants with observed C_{D151} concentrations above the estimated EC90 for RSM01 (based on available pre-clinical data) will be summarized by treatment group. Exact 95% confidence interval will be calculated on the percentages.

The same analyses will be performed for venous serum (exploratory objective).

8.4. Pharmacodynamic Concentrations

Whole blood samples on VAMS and serum samples will be collected for measurement of RSV neutralizing antibody concentrations in capillary blood and venous serum.

A listing will be prepared for each cohort with both serum and VAMS data.

9. Safety Analysis

All safety summaries and analyses will be based upon the safety population.

9.1 Adverse Events

9.1.1 Adverse Events Definitions and Reporting

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

A treatment-emergent AE (TEAE) is defined as any event not present before study intervention administration or any event already present that worsens in severity or frequency after study intervention administration.

A serious AE (SAE) is defined as any AE that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An AE of special interest (AESI) is a preidentified and predefined event that has the potential to be causally associated with a study intervention that the sponsor will carefully monitor.

The AE's relationship to study treatment will be evaluated by the investigator or medically qualified designee (ie, investigator, study physician). The following relationships will be collected on eCRF: related, not related.

The severity of AEs will be classified by the investigator as mild, moderate, severe or potentially life threatening. An overall AE summary will be generated presenting the frequency and percentage of participants and the number of AEs for the following:

- Any TEAE
- Any treatment-related TEAE
- Any grade 1 TEAE
- Any grade 2 TEAE
- Any grade 3 or higher TEAE
- Any treatment-related grade 3 or higher TEAE
- Any SAE
- Any treatment-related SAE
- Any TEAE leading to dose interruption (IV route of administration)
- Any TEAE leading to study withdrawal
- Any death
- Any AESI

All AEs will be coded using MedDRA (version to be delineated in the CSR). The TEAEs will also be summarized by system organ class (SOC), preferred term (PT), by severity and relationship to study treatment.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A participant with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of participants in the safety population (unsolicited AE) or the number of participants in the safety population that had submitted any data for a solicited AE (solicited AE).

All AEs will be presented in a data listing. Separate data listings will be generated for Severe or Life-threatening AEs, treatment-related AEs, SAEs, AEs leading to study discontinuation, Fatal AEs, AESIs, as well as a listing describing a potential association of AE with immunogenicity (ADA status).

9.1.2 Adverse Events of Special Interest (AESI)

The following AEs will be collected and reported as AESIs: anaphylaxis or hypersensitivity reactions and infusion reactions resulting in permanent discontinuation of infusion in IV recipients.

9.1.3 Solicited Local and Systemic AEs

Local injection site solicited AEs include pain, redness and swelling. If more than 1 injection is given, reactions are to be assessed separately at each injection site. All solicited local AEs will be considered study intervention related events and will be summarized for each injection site.

Systemic solicited AEs include fever, headache, tiredness, joint pain, muscle pain, nausea, vomiting and diarrhea.

All solicited AEs collected from Day 1 through Day 7 will be collected and summarized as described below.

The number and percentage of participants who experience one or more solicited AE will be summarized for each solicited AE, by treatment group, and by severity, by day after study intervention administration, and overall. The first onset of each AE, and the total number of days a participant experienced each AE will also be summarized. For participants with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Exact 95% confidence intervals will be calculated on the percentages.

Solicited local and systemic AEs will be presented in separate data listings. Ongoing AE 7 days after dosing will also be listed.

9.1.4 Unsolicited Treatment Emergent AEs, SAEs, and AESI

All unsolicited AEs, SAEs, and AESIs will be recorded from screening through Day 151.

Unsolicited AEs, SAEs, and AESIs will be coded according to MedDRA and summarized by System Organ Class (SOC), Preferred Term (PT) and highest severity. Clopper-Pearson exact 95% CIs will be calculated on the percentages of participants with AESIs. AEs leading to dose interruption for cohorts with IV route of administration and AEs leading to withdrawal from the study will also be summarized.

The number of events reported, the number of participants and percentage of participants who experience one or more unsolicited AE through Day 151, and one or more SAE, and one or more AESI from screening through Day 151 will be summarized by treatment group, as appropriate, and across all RSM01 dose levels and routes of administration, combined. The severity of each AE, and relationship between the AE and study intervention, will also be summarized.

For participants with more than 1 episode of the same event, the maximum severity will be used for tabulations. Participants reporting more than one occurrence for the PT term level being summarized will be counted only once.

9.2 Clinical Laboratory Evaluations

The following laboratory tests will be performed:

Hematology	Complete blood count (including hemoglobin, platelet count and white blood cell count) and absolute counts for neutrophils, lymphocytes, eosinophils, and monocytes.
Serum Chemistry	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, gamma glutamyl transferase (GGT), creatinine, blood urea nitrogen, lactate dehydrogenase (LDH), glucose, albumin, sodium, potassium, chloride, bicarbonate, and calcium.
Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick.
Other tests	HIV, hepatitis B and C, urine drug screen, and serum pregnancy test (females only)

The hematology, serum chemistry, and urinalysis tests will be performed at the timepoints indicated in the schedule of assessments (schedule of assessments can be found in Section 15).

All laboratory values collected at visits will be included in the summaries and listings. Descriptive summaries of observed value and change from baseline (last result available on or before Day 1) at each scheduled post baseline visit will be presented by treatment group for each continuous parameter for the safety population, both in tabular format and as boxplots. For participants who have an abnormal on-study laboratory result, longitudinal (spider) plots for hematology, serum chemistry, and urinalysis parameters will be produced.

Tables of the worst shift in FDA Toxicity Grading Scale in laboratory values from Day 1 (baseline) to visit Day 8, visit Day 91, visit Day 151 will be also presented per parameter, for those parameters that have FDA Toxicity Grading Scale grading. Values that aren't within any toxicity criteria will be presented as 'Normal'.

9.3 Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, pulse rate, and body temperature, and percent oxygen saturation and will be measured at the timepoints indicated in the schedule of assessments (see Section 15). Vital signs are to be taken after at least 5 minutes of rest in a quiet setting without distractions. Measurements are to be repeated if clinically significant changes are observed or a machine error occurs.

All vital sign, body weight, and height measurements will be presented in a data listing. The actual values and change from baseline values at each time point will be summarized by treatment group for the safety population, both in tabular format and as boxplots.

9.4 Physical Examination

A full physical examination will be conducted at screening to assess enrollment eligibility. Only participants that are considered as healthy by the investigator will be enrolled.

Physical examination at screening will include, at a minimum, assessment of height and weight, body temperature, and resting vital signs (including percent oxygen saturation by pulse oximetry), in addition to assessments needed to determine eligibility. Assessments will include general appearance and specific organ systems (head, eyes, ears, nose, throat/mouth, neck (HEENT), respiratory, cardiovascular, gastrointestinal and neurological systems, psychiatric, skin and lymphatics).

A focused physical examination will be performed to check eligibility criteria again at Visit 1 (Day 1), and subsequently if indicated by participant's medical complaint and will include assessments of body systems involved in the complaint. Focused physical examinations will be symptom directed.

Full physical examinations will be performed at Screening, and focused physical examinations will be performed at the timepoints indicated in the schedule of assessments (see Section 15).

All physical examination results will be presented in a data listing.

9.5 Electrocardiograms

A 12-lead ECG will be performed at screening using a machine that automatically calculates heart rate and determines intervals for PR, QRS, QT and QTc. Triplicate (unmarked) 12-lead ECGs will be obtained and averaged.

All 12-lead ECGs will be obtained after the participant has rested in a supine position for at least 10 minutes. All Triplicate ECGs will be taken approximately one minute apart. Measurements that deviate substantially from previous readings will be repeated immediately.

Single 12-lead ECG will be performed at the timepoints indicated in the schedule of assessments (see Section 15).

Actual values and changes from baseline for numeric ECG data will be summarized by visit and treatment group for participants in the safety population, both in tabular format and as boxplots.

Shift from baseline to the worst interpretation of ECG results (normal, abnormal (CS), abnormal (NCS) over all visits will be summarized by treatment group using the frequency count and percentage of participants in each category.

All ECG data will be presented in a data listing.

9.6 Immunogenicity

Whole blood samples on VAMS and serum samples will be collected for detection of ADA against RSM01 in capillary blood and venous serum, as specified in the schedule of assessments (Section 15). Samples on Day 1 will be collected prior to RSM01 administration.

The detection of ADA to RSM01 will be performed using a validated immunoassay method with tiered testing of screening, confirmatory, and titration. Confirmed positive antibodies may be further characterized.

ADA results will be summarized at the time of the primary analyses, when all participants reach Day 151. The following analyses will be conducted separately for both VAMS (secondary objective) and serum (exploratory objective).

The overall analysis of immunogenicity will focus on the following key parameters:

- Immunogenicity incidence and characterization
- Association with pharmacokinetics
- Association with TEAEs

The immunogenicity population used in the analysis is described in Section 4.4.

9.6.1 Terms and Definitions

The detection of ADA to RSM01 will be performed using a validated immunoassay method with tiered testing of screening, confirmatory, and titration, i.e.:

1. All samples will undergo a screening test.
2. If the screening test is positive for ADA, the sample will undergo a confirmatory test. A sample that has a negative or not reportable (NR) screening result will not undergo further testing.
3. If the confirmatory test is positive, the sample will be analyzed to determine the titer. A titer result can be a quantifiable number or not reportable ("titer not reportable" or "TNR").

The following terms and definitions will be applied in the immunogenicity analyses.

ADA status of a sample

- Baseline ADA negative sample: Screening or confirmatory test of the last sample before administration of study treatment indicates ADA is not detected.
- Baseline ADA NR sample: Screening or confirmatory test of the last sample before administration of study treatment indicates ADA is not reportable.
- Baseline ADA missing: No baseline sample was available for testing.
- Baseline ADA positive sample: Screening and confirmatory tests of the last sample before administration of study treatment indicates ADA is detected. The numeric titer will be reported unless the titer result is NR, which would be reported as positive TNR.
- Post-baseline ADA negative sample: Screening or confirmatory test of sample taken after administration of study treatment indicates ADA is not detected.

- Post-baseline ADA NR sample: Screening or confirmatory test of sample taken after administration of study treatment indicates ADA is not reportable.
- Post-baseline ADA missing: No post-baseline sample was obtained.
- Post-baseline ADA positive sample: Screening and confirmatory tests of sample taken after administration of study treatment indicates ADA is detected. The numeric titer will be reported unless the titer result is NR, which would be reported as positive TNR.

ADA status of a participant

- Baseline ADA negative participant: A participant with baseline ADA negative sample. A participant with NR or no baseline ADA sample is assumed to be baseline ADA negative.
- Baseline ADA positive participant: A participant with a baseline ADA positive or positive TNR sample.
- Post-baseline ADA positive participant: A participant with at least one post-baseline ADA positive or positive TNR sample. An ADA positive participant will be further classified as follows:
    - Treatment-emergent positive: Participant had a post-baseline ADA positive or positive TNR sample in a participant with a baseline ADA negative sample OR participant had a post-baseline ADA positive sample that is ≥ 8-fold increase above baseline titer in a participant with a baseline ADA positive sample. Note that the baseline sample and at least one post-baseline sample must have reportable titer to assess whether pre-existing immunogenicity was treatment-boosted.
    - Treatment-emergent nonevaluable.
    - Treatment-emergent negative.
- Post-baseline ADA negative participant: A participant with no post-baseline ADA positive or positive TNR sample.
- Any ADA detected: Subjects in Baseline ADA Positive AND/OR Treatment-emergent.
- No ADA Detected: Subjects who are Baseline ADA negative AND either Post-baseline ADA negative OR no valid post-baseline results (excluded from immunogenicity population).

9.6.2 Derivation Rules

Based on the definitions provided in Section **Error! Reference source not found.**, immunogenicity results will be collected prior to dose administration and at post-treatment follow-up visits. Immunogenicity results will be collected prior to dose administration and at post-treatment follow-up visits. Sample-level and participant-level derivations are shown in Tables 1 and 2, respectively.

Table 1: Algorithm for Deriving of Anti-Drug Antibody Sample-Level Results

SDTM raw data			**Derived ADaM sample result**
ADA Screening Result (ISTSTOPO=Screen)	**ADA Confirmatory Result (ISTSTOPO=Confirm)**	**ADA Titer Result (ISTSTOPO=Quantity)**	
Negative	NA	NA	Negative
NR	NA	NA	NR
Missing	NA	NA	Negative
Positive	Negative	NA	Negative
Positive	NR	NA	NR
Positive	Positive	Number	Number
Positive	Positive	NR	Positive TNR

ADaM = analysis data model, NA = not applicable, NR = not reportable, SDTM = study data tabulation model, TNR = titer not reportable.

Table 2: Algorithm for Deriving Anti-Drug Antibody Participant-Level Results

ADaM data across samples		**Participant-level ADaM result**		
Baseline ADA result	**Post-baseline ADA results**	**Derived baseline ADA**	**Derived post-baseline ADA**	**Treatment-emergent**
Negative or NR or Missing	At least one Negative, no Number or Positive TNR	Negative	Negative	Negative
Negative or NR or Missing	All NR or Missing	Negative	NA	NA
Negative or NR or Missing	At least one Positive TNR, no Number	Negative	Positive TNR	Treatment-emergent
Negative or NR or Missing	At least one Number	Negative	Positive	Treatment-emergent
Positive TNR	At lease one Negative, no Number of Positive TNR	Positive TNR	Negative	Neither
Positive TNR	All NR or Missing	Positive TNR	NA	NA
Positive TNR	At least one Positive TNR, no Number	Positive TNR	Positive TNR	TNR
Positive TNR	At least one Number	Positive TNR	Positive	TNR
Number	At least one Negative, no Number or Positive TNR	Positive	Negative	Negative
Number	All NR or Missing	Positive	NA	NA
Number	At least one Positive TNR, no Number	Positive	Positive TNR	TNR
Number	At least one Number, but none ≥	Positive	Positive	Negative

ADaM data across samples		Participant-level ADaM result		
Baseline ADA result	**Post-baseline ADA results**	**Derived baseline ADA**	**Derived post-baseline ADA**	**Treatment-emergent**
	8-fold increase above baseline titer			
Number	At least one Number ≥ 8-fold increase above baseline titer	Positive	Positive	Treatment-emergent

ADaM = analysis data model, NA = not applicable since not in immunogenicity population, NR = not reportable, SDTM = study data tabulation model, TNR = titer not reportable.

The number and percentage of participants will be reported as follows:

- Baseline ADA positive vs. negative in the Immunogenicity Population
- Post-baseline ADA positive among participants with at least one post-baseline ADA sample
    - Treatment-emergent ADA
    - Negative treatment-emergent

Listings will be prepared with ADA sample-level and participant-level results.

9.6.3 Potential Association of Immunogenicity with Adverse Events

A summary of AEs showing frequency and percentage of participants with AEs will be produced for the following subgroups:

- Any ADA detected
- No ADA detected

10. Missed Assessments due to COVID-19

All visits or assessments missed due to COVID-19 will be presented in a listing.

11. Interim Analysis

An interim analysis is planned after availability of Cohort 2, Cohort 3, and Cohort 4 Day 30 data.

An interim analysis with a formal Safety report is planned for this study when all participants in each of the Dose Escalation Phase cohorts have completed Day 91. In addition, SDTM datasets will be prepared for interim PK modeling. An Interim Report will be prepared when the results from Day 91 become available. Additional interim analyses may occur prior to the primary analysis to aid in the development of individual and population PK models to predict dose levels in infants and assess covariates.

The purpose of this interim analysis will be a strategic review to inform the broader program and future development plans, including the determination of the potential dose of RSM01 in infants. No decision directly related to this study will be made from the results of this interim analysis. Agreement on the analysis plan, unblinding procedures, specific outputs, method of distribution,

the level of data cleaning and details of whom the results will be provided to will be outlined in a separate unblinding plan (which will be finalized prior to the interim analysis).

Firewalled roles will be involved in the interim analysis to create unblinded datasets and perform analyses. The investigator will remain blinded. The sponsor will review blinded (pooled) safety data by cohort and unblinded aggregated PK data by treatment group (RSM01 vs. placebo) within and across cohorts. The sponsor will be blinded at the participant level throughout the study. An unblinding plan will be prepared to include unblinding details.

12. Changes in the Planned Analysis

Any changes from this statistical analysis plan that are not documented in a formal SAP amendment will be documented in the CSR for this study.

13. Change of Statistical Programming Service Provider

In May 2022, Gates MRI decided to terminate the RSM01-101 biostatistics and statistical programming contract with its original service provider. Gates MRI assumed responsibility for statistical oversight of the study, including finalization of the SAP, and initiated a new agreement with another service provider for the statistical programming of SDTM and ADaM datasets as well as tables, figures, and listings. In its statistical oversight, Gates MRI will follow statistical principles that are consistent with the International Conference on Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials) and apply the following procedures:

- Prior to an interim unblinded data review, Gates MRI will finalize an unblinding plan that describes the purposes for unblinding, the roles and responsibilities of team members who will be involved in the unblinding steps and the preparation and review of unblinded analyses, and the level of access each role will have to unblinded interim data (i.e., fully blinded, blinded except emergency participant-level unblinding, unblinded to aggregate results, or unblinded to participant-level results);

- Prior to an interim unblinded data review, Gates MRI will finalize a statistical analysis plan that describes all analyses that will be included in the clinical study report; and

- Gates MRI will rely on the new service provider to initiate unblinding as described in their SOP, including use of the new service provider's unblinding authorization form.

Gates MRI is currently in the process of establishing SOPs associated with unblinding and statistical analysis plans.

New data transfer agreements have been established to allow blinded and unblinded data transfers between Gates MRI and the data management, statistical programming, and PK vendors, as described in a separate Unblinding Plan. All of the service providers have continued to follow their respective standard operating procedures (SOPs) for establishing and maintaining the necessary firewalls to protect the study blind.

14. References

Protocol Gates MRI-RSM01-101. A Phase 1 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of RSM01, a Monoclonal Antibody Targeting Respiratory Syncytial Virus, in Healthy Adults, Protocol Version 4.0, 21 Jan 2022.

FDA, Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (Silver Spring, MD, August 2014).

EMA, Guideline on Immunogenicity assessment of therapeutic
Proteins – Revision 1 (London, UK, May 2017).

15. Schedule of Assessments

Schedule of Activities for the Dose Escalation Phase (Cohorts 1-4)

Visits	Screen	Pre-V1	V1	V2	V3	V4	V5	V6	V 7	V8	V9	V10	V11	Dis-con
Study Day and Visit window days (d)	D-30 to D-2d	D-1 ±0d	D1 ±0d	D2 ±0d	D3 ±0d	D6 ±1d	D8 Day 8-10	D15 ±3d	D2 9 Day 29-35	D61 ±7d	D91 ±7d	D121 ±7d	D151 ±7d	Visit[9]
Activities:														
Informed consent	X													
Check/verify eligibility criteria	X	X	X											
Confinement[1]		X	X	X	X									
Demography, full medical history, PE, height, weight	X													
Focused PE		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[2]	X	X												X
HIV antibody and Hepatitis B & C test	X													
Urine drug screen	X	X												
Urinalysis	X	X					X				X		X	X
Safety laboratory assessments[3]	X	X					X				X		X	X
12-lead electrocardiogram (ECG), performed intriplicate[4]	X			X										
Vital signs[5]	X		X	X	X									X
Randomization[6]			X											
Study intervention administration[7]			X											
Distribute/review diary cards					X									
Collect diary card							X							
Distribute memory aid					X	X	X	X	X	X	X	X		
Collect memory aid						X	X	X	X	X	X	X	X	X
Record solicited AEs (local for IM doses only, &systemic) through Day 7			X	X	X	X								
Record unsolicited AEs, AESIs, and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Activities for the Dose Escalation Phase (Cohorts 1-4)

Visits	Screen	Pre-V1	V 1	V 2	V 3	V 4	V 5	V 6	V7	V 8	V 9	V1 0	V11	Dis-con Visit[9]
Study Day and Visit window days (d)	-30 to -2d	D-1	D1 ±0d	D2 ±0d	D3 ±0d	D6 ±1d	D8 Day 8-10	D15 ±3d	D29 Day 29-35	D61 ±7d	D91 ±7d	D121 ±7d	D151 ±7d	
Activities:														
Serum and VAMS sample for PK[8]			X	X	X	X	X	X	X	X	X	X	X	X
Serum and VAMS sample for ADAs[8]			X					X	X	X	X	X	X	X
Serum and VAMS sample for RSV nAb levels[8]			X								X		X	X

V = Visit; D= Day; PE= physical examination; HIV= Human immunodeficiency virus; IM= intramuscular; AE=adverse event, SAE=serious adverse event; AESI=AE of special interest; PK= pharmacokinetics; ADA = anti-drug antibodies; VAMS = volumetric absorptive microsampling RSV mAb = Respiratory Syncytial Virus neutralizing antibody

[1] Confinement- participants will be confined to study site from Day -1 to after completion of Day 3 assessment (a total of 3 nights). All Day 1 assessments and sample collections are prior to study intervention.

[2] In addition to scheduled pregnancy tests in female participants, if pregnancy is suspected during the study, a serum test will be done.

[3] Safety laboratory testing includes serum chemistry and hematology.

[4] All 12-lead ECGs will be obtained after the participant has rested in a supine position for at least 10 minutes. Triplicate ECGs will be taken approximately one minute apart. Refer to Protocol section 8.1.6 for details. The window for obtaining the initial ECG is ± 15 minutes.

[5] Day 1 vital signs will be taken pre-dose before blood sample collection, and 1 hour, 4 hours and 8 hours after IM dose and at pre-dose, 15, 30 and 45 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, and 8 hours after IV dose. The window for vital signs measurements is ± 3 minutes. Refer to Protocol section 8.1.2.1. Vital Signs for details. On Day 2, vital signs will be taken at 24 hours post-dose. The window for these measurements is ± 0.5 hours. On Day 3, vital signs will be taken at 48 hours after dosing. The window for these measurements is ± 1.0 hours.

[6] The first participant in each cohort (Cohorts 1-4) will receive RSM01without being randomized.

[7] On any given day, participants should be dosed at least 2 hours apart, after the first sentinel participant is dosed with RSM01, and 24 hours has passed. The ≥2-hour wait time between IV infusions is to begin at the end of the previous infusion.

[8] Blood samples for PK assessments on Day 1 (Visit 1) will be drawn at pre-dosing 1 hour (+/- 30 minutes) before administration of IM injection or beginning of infusion,, at 5 minutes (± 1 minute) after end of infusion for IV doses only, and at 8-hours (±0.5 hour) and 24-hours (±1 hour) after end of infusion for IV doses and at 8-hours (±0.5 hour) and 24-hours (±1 hour) after IM doses. ADA and RSV neutralizing antibody on Day 1 (Visit 1) will be drawn pre-dose only 1 hour (+/- 30 minutes) before administration of IM injection or beginning of infusion.

9 Early Discon= A discontinuation visit will be scheduled for participants who discontinue or withdraw, whenever possible.

Schedule of Activities for the Expansion Phase (Cohort 5)

Visits	Screen	Pre-V1	V 1	V 2	V 3	V 4	V 5	Discon visit[8]
Study Day and Visit window days (d)	D-30 to D-1d	**Day -1**	**D1**	**D8**	**D29**	**D91**	**D151**	
Activities:			±0	Days 8-10	Days 29-35	±7d	±7d	
Informed consent	X							
Check/verify eligibility criteria	X	X	X					
Confinement[1]		X	(X)					
Demography, full medical history, PE, height, weight	X							
Focused history/PE			X	X	X	X	X	X
Serum pregnancy test[2]	X	X						X
HIV antibody, Hepatitis B and C	X							
Urine drug screen	X	X						
Urinalysis	X	X		X		X	X	X
Safety laboratory assessments[3]	X	X		X		X	X	X
12-lead ECG (performed in triplicate)[4]	X							
Vital signs[5]	X		X					X
Randomization			X					
Study intervention administration[6]			X					
Distribute/review diary cards			X					
Collect diary cards				X				
Distribute memory aid			X	X	X	X		
Collect memory aid				X	X	X	X	X
Record solicited AEs (local & systemic)			X					
Record unsolicited AEs, AESIs and SAEs	X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X
Serum and VAMS sample for PK[7]			X	X	X	X	X	X
Serum and VAMS sample for ADAs[7]			X		X	X	X	X
Serum and VAMS for RSV nAb levels[7]			X			X	X	X

V = Visit; D= Day; PE= physical examination; HIV= Human immunodeficiency virus; IM= intramuscular; AE=adverse event, SAE=serious adverse event; AESI=AE of special interest; PK= pharmacokinetics; ADA = anti-drug antibodies; VAMS = volumetric absorptive microsampling; RSV mAb = Respiratory Syncytial Virus neutralizing antibody

[1]Confinement = participant should present to the clinic within 24 hours of Day -1 visit and will stay at the clinic on the Pre-V1, Day -1(i.e., the night before the Day 1 visit). (X)= A second overnight stay for the night of Day 1 is optional, based on investigator's decision. If participant is confined on the night of Day 1, vital signs will be taken 24 hours post-dose.

[2] In addition to scheduled pregnancy tests in female participants, if pregnancy is suspected at any time during the study, a serum test will be done.

[3] Safety laboratory assessments includes serum chemistry and hematology.
[4] 12-lead ECGs will be obtained after the participant has rested in a supine position for at least 10 minutes. Triplicate ECGs will be taken approximately one minute apart. Refer to Protocol section 8.1.6 for details.
[5] Day 1 vital signs will be taken before dose and again 4 hours after dose. The window for vital signs measurements is ± 3 minutes. Refer to Protocol section 8.1.2.1. Vital Signs for details.
[6] All Day 1 safety assessments and sample collections will be done prior to study intervention. Symptom assessments will be done after dosing. Following dose administration, if the participant will not be confined overnight for the optional night of Day 1, they will be observed for at least 4 hours at the study site after receiving the study intervention, for safety monitoring.
[7] Blood samples for PK, ADA and RSV neutralizing antibody at Day 1 will be drawn at pre-dose only 1 hour (+/- 30 minutes) before administration of IM injection.
[8] Early Discon = A discontinuation visit will be scheduled for participants who discontinue or withdraw, when possible.