Title Page

Protocol Title: 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 Number: Gates MRI-RSM01-101, Version (v)4.0

Short Title: Safety, Tolerability, and Pharmacokinetics of RSV Monoclonal Antibody RSM01 in Healthy Adults

Compound Number: RSM01

Study Phase: 1

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Refer to Section 12 for the rationale for v4.0 and a complete list of changes.

Sponsor Signature Page

Version 3.0

See appended electronic signature page

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Sponsor Signatory Date

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List of Abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the (time) curve (e.g., capillary blood-concentration time curve for RSM01)
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
CFR	Code of Federal Regulations
CL	Systemic clearance
CRF	Case report form
CSR	Clinical study report
EC_{90}	Effective concentration that leads to 90% maximal response (or the logarithm of the $EC9_0$)
ECG	Electrocardiogram
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
GCP	Good clinical practices
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
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
IXRS	Interactive voice/web response system
LTRI	Lower respiratory tract infection
mAb	Monoclonal antibody
Mg	Milligram
mL	Milliliter
mITT	Modified intention to treat
NA	Not applicable
NCA	Noncompartmental analysis
NCT	National (U.S.) Clinical Trial Identifier
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol

Pre-F	Prefusion conformation of the Respiratory Syncytial Virus F glycoprotein
RSM01	Monoclonal antibody targeting Respiratory Syncytial Virus, Drug Product for use in the clinical trial
RSV	Respiratory Syncytial Virus
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of activities
SRT	Safety Review Team
t1/2	Apparent terminal half-life
T_{max}	Time to maximum capillary blood-concentration of RSM01
ULN	Upper limit of normal
U.S.	United States
VAMS	Volumetric absorptive microsampling
Vz	Volume of distribution
WBC	White blood cell count
WHO	World Health Organization
YTE	Triple amino acid substitutions

1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Short Title: Safety, Tolerability, and Pharmacokinetics of RSV Monoclonal Antibody RSM01 in Healthy Adults

Rationale: 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 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.

Proof of concept for passive immunization of infants with a mAb has been demonstrated for palivizumab, a commercial mAb product indicated to prevent RSV disease in premature infants. Palivizumab, however, must be administered monthly during the RSV season and is very costly.

Two (2) next generation RSV mAb candidates are in clinical development: Merck's MK-1654 and AstraZeneca's MEDI8897 (nirsevimab). In completed trials, nirsevimab shows promise in reducing the incidence of medically-attended lower respiratory tract infection (LRTI) and hospitalizations caused by RSV, in healthy preterm infants. Both of these 2 mAb candidates were well-tolerated. Regardless, the cost of these candidates when commercialized may not allow for global access to the product.

RSM01 is a fully human IgG1 mAb that targets glycoprotein F of RSV and binds to the antigenic site Ø of the prefusion conformation of the F protein (a region considered to be highly sensitive to neutralization). The major mode of action for RSM01 is virus neutralization. RSM01 has the same half-life extension, triple amino acid substitutions (YTE) M252Y/S254T/T256E (European Union numbering), mutation in its crystallizable fragment (Fc) domain, as do the MK-1654 and nirsevimab RSV mAb candidates.

In this study, healthy adults will receive either intravenous (IV) or intramuscular (IM) doses of RSM01, which will enable assessment of the safety profiles together with estimation of human bioavailability following IM injection, which is the intended route of administration in infants.

Table 1: Objectives and Endpoints

Objectives	**Endpoints** *(Endpoints apply to all cohorts unless noted)*
Primary	
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 • Solicited local AEs for injection site reactions for 7 days after dose administration (only applies to IM doses)
Secondary	
To characterize safety laboratory parameters following RSM01 administration	• Safety laboratory parameters Grade 1 and above 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 ($AUC_{0-\infty}$) • Day 91 capillary blood-concentration and area under the capillary blood-concentration time curve (C_{D91} and AUC_{0-D91}) • Day 151 capillary blood-concentration and area under the capillary blood-concentration time curve (C_{D151} and AUC_{0-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}) apparent terminal half-life (t1/2) • Systemic clearance (CL) • Volume of distribution (Vz) of RSM01 through Day 151
To characterize the formation of anti-drug antibodies (ADAs) following RSM01 administration	• Incidence of ADAs to RSM01 through Day 151
Exploratory	
To characterize RSV neutralizing antibody activity following RSM01 administration	• Capillary blood RSV neutralizing antibody levels through Day 151

Overall Design

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

Study Population and Number of Participants: Adult participants between 18 and 49 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent may be eligible for the study.

Candidates will be screened to enroll at least 56 eligible participants.

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

Interventional model*:* 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.

Dose Escalation Phase:

The Dose Escalation Phase will include 28 participants.

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 occur sequentially in 2 escalation steps.

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

First escalation step: from Cohort 1 to Cohorts 2 and 3, conducted in parallel

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

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

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

For the Dose Escalation Phase cohorts, all participants will be confined at the study site from Day -1 (i.e., the day before dosing) to after completion of the Day 3 assessments (a total of 3 nights).

After the sentinel participant in each cohort receives RSM01, the next participant can be dosed 24 hours later, if there is no safety concern. After the 24-hour post-dose period for the sentinel participant in each cohort, participants in the Dose Escalation Phase cohorts should be dosed at least 2 hours apart regardless of route of administration (IM or IV). The ≥2-hour interval between administering IV infusions is to begin at the end of the previous infusion. For participants receiving the IM dose of study drug in Cohort 2, the ≥2-hour interval between administering IM injections to successive participants is to begin at the time of the previous

participant's IM injection. If RSM01 is administered using 2 injections, the ≥2-hour interval begins at the time of the second injection.

Each dose escalation step will proceed after all participants in the prior cohort have completed Day 15, and the Safety Review Team (SRT) has reviewed the data and determined that a pausing rule has not been met.

Dose Expansion Phase:

Enrollment in the Dose Expansion Phase cohort (Cohort 5) will begin after Day 15 for all participants in Cohort 4, and after the SRT has reviewed the data and determined that a pausing rule has not been met. Cohort 5 will include 28 participants randomized 6:1.

- Cohort 5: participants will receive RSM01 IM (n=24) or Placebo IM (n=4).

For Cohort 5, participants will be asked to present to the clinic within 24 hours of the Day 1 visit for Day -1 (Pre-V1) confinement.

On Day 1 after dosing, participants will be observed for at least 4 hours post-dose at the study site for safety monitoring. Based on investigator's decision, a participant may be asked to remain at the study site, for an additional overnight stay on the night of Day 1.

Final selection of the dose of RSM01 to be administered to Cohort 5 will be made by the sponsor and informed by available RSM01 PK data from the Dose Escalation Phase.

The tentatively determined dose to be evaluated in the Expansion Phase cohort is ≥300 mg to ≤600 mg IM. This determination is based on predictions of RSM01 human PK exposures made using extrapolation from the RSM01 non-human primate PK and on published data from the other RSV mAbs nirsevimab and MK-1654 administered to healthy adults [Griffin 2017, Aliprantis 2020]. The predictions suggest that the concentration of RSM01 will be above the efficacy threshold (EC90) on Day 151 following a RSM01dose of 300 or 600 mg IM.

Pausing Rules

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 toxicity 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 and the U.S. Food and Drug administration (FDA) will be notified in an expedited manner.

IDMC: The IDMC will review safety data if a pausing rule is met and make a recommendation on how to proceed (See Section 8.2.7.). The IDMC will be provided unblinded data by an independent statistician.

Safety Review Team: A SRT will be established as the team responsible for recommending dose escalation or dose expansion to the sponsor's Chief Medical Officer. Meetings of the SRT to provide a recommendation on dose escalation or dose expansion will occur during the Dose Escalation Phase when all participants in the currently dosed cohort have completed Day 15. The SRT will also meet approximately every 8 weeks during the Dose Expansion Phase (See Section 8.2.6). The SRT will review blinded data only.

Visits: After the Screening Visit, and the Day -1 Visit, 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.

Note that when participants arrive for the Day -1 clinic visit, they will stay overnight at the clinic. Participants in the Dose Escalation Phase cohorts will remain at the clinic for Visits 1, 2, and 3, on Day 1, Day 2, and Day 3, respectively.

The participants in the Dose Expansion Phase cohort will remain at the clinic for at least 4 hours after dosing on Day 1, and possibly for the night of Day 1, based on investigator's decision.

The study Schema is shown in Figure 1 and the Schedule of Activities (SoA) is shown in Table 2, and Table 3 for Dose Escalation Phase and Dose Expansion Phase, respectively.

Blood Sampling: Dose Escalation Phase cohorts: On Day 1, PK blood draw will occur **pre-dosing** 1 hour (+/- 30 minutes) before administration of IM injection or beginning of IV infusion**,** at 5 minutes (± 1 minute) after end of infusion for IV dosing 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 dose. ADA and RSV neutralizing antibody activity samples will be obtained pre-dose only 1 hour (+/- 30 minutes) before administration of IM injection or beginning of IV infusion.

Dose Expansion Phase cohort: On Day 1, the blood collection for PK, ADA and RSV neutralizing antibody activity will occur pre-dosing only 1 hour (+/- 30 minutes) before administration of IM injection.

Serum will be collected as shown in the SoA (Section 1.3), for screening and safety laboratories. Venous serum and capillary volumetric absorptive microsampling (VAMS) will be collected as shown in the SoA (Table 2 and Table 3) for PK, ADA testing and RSV neutralizing antibody testing.

A maximum of approximately 200 mL of whole blood will be collected from each participant during the entire study period, assuming all planned samples are collected, according to the SoA.

Masking: The study is double-blind. Participants and all study personnel will be blinded to the randomization, with one exception: the first sentinel participant in each Dose Escalation Phase

cohort will be single-blinded (participant-blinded) and will receive the respective dose of RSM01. Authorized study site personnel will administer doses.

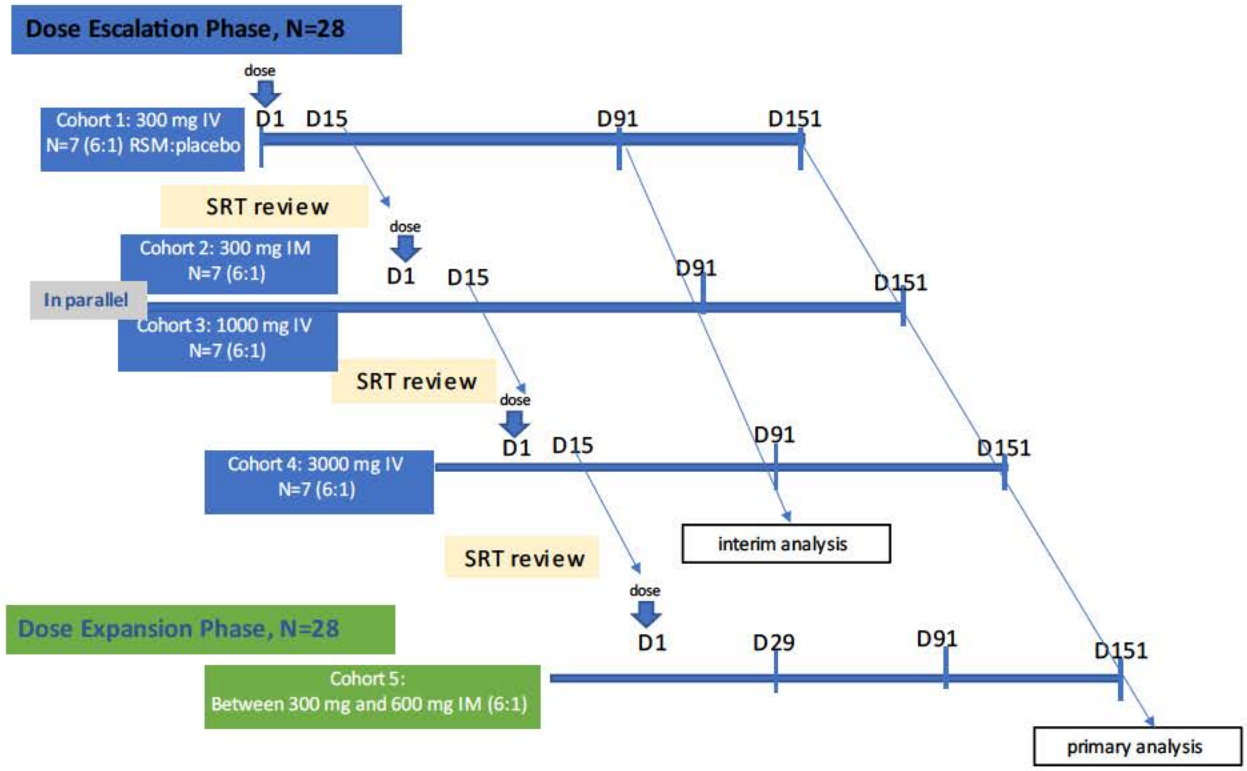
Analysis: An interim analysis will occur after all participants in the Dose Escalation Phase cohorts (Cohorts 1 through 4), have reached Day 91. The primary analysis will occur after all participants in all 5 cohorts complete Day 151.

Total duration of study participation: The study duration for each participant is 151 days, in addition to a maximum of 30 days for screening and Day -1.

Study site/s: The study will be conducted at 1 site in the United States (U.S.).

1.2. Schema

Figure 1: Outline of Study Dosing Procedures



1.3. Schedule of Activities (SoA)

The SoA for the Dose Escalation Phase (Cohorts 1-4) is presented in Table 2 and the SoA for the Expansion Phase (Cohort 5) is presented in Table 3.

Table 2: Schedule of Activities for the Dose Escalation Phase (Cohorts 1-4)

Visits	Screen	Pre-V1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Dis-con Visit[9]
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	D29 Day 29-35	D61 ±7d	D91 ±7d	D121 ±7d	D151 ±7d	
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), triplicate[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

Table 2 continued: Schedule of Activities for the Dose Escalation Phase (Cohorts 1-4)

Visits	Screen	Pre-V1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	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 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 Section 8.1.2.1for 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.

Table 3: 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

[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.
PK= pharmacokinetics; ADA = anti-drug antibodies; VAMS = volumetric absorptive microsampling;
RSV mAb = Respiratory Syncytial Virus neutralizing antibody

[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 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 Section 8.1.2.1for 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.

2. Introduction

2.1. RSV and Burden of Disease

RSV is the most common pathogen identified in young children with acute LRTI. Most children acquire an RSV infection by the time they are 2 years old, causing a mild, cold-like illness within 4 to 6 days after infection. However, in some children it leads to a more severe illness such as bronchiolitis and pneumonia and may also increase the risk of developing subsequent asthma and/or recurrent wheezing episodes in early childhood. The highest childhood RSV acute LRTI burden occurs during the first year of life when children are most vulnerable.

RSV is a global disease that also places high burdens on the economy and health care services. Estimates show that approximately 33.1 million episodes occurred globally in 2015, resulting in about 3.2 million hospital admissions in children younger than 5 years, and 1.4 million hospitalizations in children younger than 6 months. Healthy term infants 3 months of age and younger account for more RSV-associated hospitalizations than any other age group. The hospital admission rate from RSV in LMICs is 15.9 per 1000 neonates per year with incidence rates being 3 times greater in preterm than term infants [Shi 2017].

Globally, there are approximately 120,000 RSV-associated acute LRTI deaths among children <5 years of age each year [Obando-Pacheco 2018] which account for a third of all LRTIs, with most deaths occurring in LMICs [Shi 2017]. Approximately 45% of in-hospital deaths due to RSV-associated acute LRTI occur in children younger than 6 months (median age of RSV-related deaths is 4-7 months [Shi 2017, Scheltema 2017]), indicating that these infants constitute a critically important target group for prevention. However, the need for immediate protection and the difficulty of achieving protective efficacy via active immunization of these infants have refocused research efforts toward maternal immunization and passive immune-prophylaxis as key priorities. Either of these strategies could be followed with active infant immunization later in life as maternal/passive antibody titers wane [Higgins 2016].

The burden of RSV infection, especially among infants and young children, underscores the need for safe and effective prevention against RSV disease that is affordable in LMICs.

2.2. RSV Prevention- Monoclonal Antibodies

There is an unmet medical need for an effective, durable, cost effective RSV prevention strategy for all infants and children. The World Health Organization (WHO) Product Development for Vaccines Advisory Committee (PDVAC) indicates that RSV immunoprophylaxis with a monoclonal antibody (mAb) is a priority intervention. There is no approved vaccine against RSV currently- the majority of candidates in clinical evaluation incorporate alternative antigens or constructs and target maternal or pediatric immunization strategies.

Administration of a mAb directly to the infant at birth or at any time during the primary immunization series presents an attractive alternative to maternal immunization. The mAb would only need to be used in infants up to 6 months of age or those at risk of LRTIs during the local RSV season, which would reduce the overall programmatic cost of RSV disease prevention. Critical success factors intrinsic to a candidate mAb include high potency, product safety, high barrier to virus resistance, and stability / PK that gives adequate duration of protection.

There is one approved RSV mAb, palivizumab, which is indicated for the prevention of serious LRTI caused by RSV and has been used in the past 2 decades. Palivizumab is an RSV fusion (F)-specific immunoglobulin G monoclonal antibody (Synagis®, Swedish Orphan Biovitrum) that requires monthly injections and is cost prohibitive for LMICs. It is approved for use in high-risk children, including 1) preterm infants born at ≤ 35 weeks gestational age and who are ≤ 6 months old at the beginning of RSV season; 2) children with bronchopulmonary dysplasia that required medical treatment within the previous 6 months and who are ≤ 24 months old at the beginning of RSV season; and 3) children with hemodynamically significant congenital heart disease and who are ≤ 24 months old at the beginning of RSV season. Among preterm infants, the American Academy of Pediatrics issued an updated guidance in 2014 to limit its recommendation for palivizumab to preterm infants born before 29 weeks gestational age and who are ≤ 12 months old, who would most likely benefit from this preventive agent [Brady, 2014].

Motavizumab, a derivative of palivizumab with higher affinity for RSV, was not pursued by MedImmune for licensure after the Phase 3 trial failed to secure FDA approval for lack of clear superiority to palivizumab and a trend for a higher rate of skin rash [Feltes, 2011]. A mAb manufactured by Regeneron (REGN2222 or suptavumab) did not meet efficacy endpoints in Phase 3, and clinical development was also discontinued. This was due to escape mutants in the predominantly circulating RSV B that affected the overall performance of REGN2222 [Simões 2020].

Two other RSV mAbs are in clinical development, with MEDI8897 (nirsevimab), being the most advanced. Nirsevimab binds to the same antigenic site Ø of RSV prefusion F but different epitope than RSM01. In a Phase 2b trial of 1453 premature infants 29- to 34-week gestational age who were ≤1 year old, nirsevimab administration reduced the incidence of RSV-associated medically-attended LRTI by 70% and hospitalizations by 78% compared to Placebo [Griffin 2020]. The nirsevimab program has initiated enrollment of a Phase 2b/3 in preterm infants ≤35 weeks gestational age with either chronic lung diseases or congenital heart disease or bronchopulmonary dysplasia [Clinicaltrials.gov NCT No. 03959488], and a Phase 3 study in term and late preterm infants ≥35 weeks gestational age [Clinicaltrials.gov NCT No. 03979313].

The primary endpoint of a statistically significant reduction in the incidence of medically-attended RSV LRTIs was met in this trial [AstraZeneca 2021].

The other RSV mAb candidate, MK-1654, targets site IV of the RSV pre- and post-fusion F. A Phase 2 study of safety and PK study in infants is ongoing [Clinicaltrials.gov NCT No. 03524118]. An RSV challenge study in healthy adults was completed in August 2020 and no results are available to date [Clinicaltrials.gov NCT No. 04086472]. However, these mAb candidates in development are targeted primarily for high-income countries, with costs likely too high to allow affordable global access to the product.

Evidence from the Novavax maternal RSV F nanoparticles vaccine trial suggests that prevention of RSV early in life can also result in 25% reduction in all-cause LRTI hospitalization up to one year of age [Madhi 2020]. An efficacious RSV immunization product could have significant public health impact in preventing pneumonia deaths in young infants, with potential benefits that may extend longer.

2.3. RSM01 mAb Candidate

RSM01(also designated as ADI-15618-IVNS YTE) is a fully human IgG1 neutralizing monoclonal antibody that targets site Ø (zero) of the prefusion conformation of the RSV F glycoprotein (pre-F), which has high neutralizing potency. RSM01 has a molecular weight of approximately 150 kilodaltons.

RSM01 has the same half-life extension YTE mutation (M252Y/S254T/T256E, European Union numbering) in its crystallizable fragment (Fc) domain as 2 other next generation RSV mAb candidates, Merck's MK-1654 and AstraZeneca's nirsevimab, which are being evaluated in Phase 2 and 3 clinical trials, respectively. Both have a favorable safety profile in previous clinical trials [Aliprantis 2020, Griffin 2017], and nirsevimab was shown to reduce the incidence of RSV-associated medically-attended LRTI and hospitalizations in a Phase 2b study [Griffin 2020].

2.3.1. Non-Clinical Development of RSM01

The non-clinical development of RSM01 focused on non-clinical safety studies in rats and monkeys, in vitro potency against RSV A and B assessments and efficacy studies in a cotton rat RSV challenge model. These studies are considered sufficient to support entry into Phase 1 FiH study in adults, followed by age de-escalation into a Phase 1b/2a study in infants.

The non-clinical pivotal safety package for RSM01 conducted to support FiH studies consists of a 4-week Good Laboratory Practice (GLP) study in monkeys and a cross-reactivity GLP study in human tissues.

Overall, RSM01 was well-tolerated in non-GLP single dose studies in rats and monkeys, and in a 4-week repeat-dose GLP study in cynomolgus monkeys. In the 4-week study, RSM01 was administered weekly plus one for a total of 5 doses at 30, 100, and 300 mg/kg, IV and at 100 mg total dose in 1mL, IM. There were no identified target organs of toxicity or test-article-related adverse local reactions; there were also no test-article-related effects on the cardiovascular, respiratory or the central nervous systems at all doses The No-Observed-Adverse-Effect-Level (NOAEL) in the 4-week study was 300 mg/kg/dose, IV (area under the curve $[AUC]_{0\text{-}168h}$:1,420,000 µg*h/mL; C_0: 11,900 µg/mL) and 100 mg/dose, IM ($AUC_{0\text{-}168h}$:264,000 µg *h/mL; maximum plasma concentration [C_{max}]:1760 µg/mL). A tissue cross-reactivity study with biotinylated RSM01 found no risk for off-target binding of RSM01 in human tissues. The non-clinical safety profile of RSM01 supports dosing of humans in Phase I clinical trials. No local toxicity was observed in monkeys following IM administration at the same concentration of mAb (approximately 100 mg/mL) intended for use in humans.

The NOAEL of 300 mg/kg, IV supports a Maximum Recommended Starting Dose (MRSD) of 582 mg [FDA 2005] with an applied safety factor of 10. This supports the proposed starting dose of 300 mg, IV, in adults.

In vitro cell-based neutralization studies showed that RSM01 performed as well or better than other RSV mAbs to neutralize both RSV A and RSV B clinical isolates including important sequence variants that are critical for epitope binding. RSM01 potency was comparable to that of nirsevimab and more potent than REGN2222 and palivizumab.

In cotton rat challenge studies, RSM01 reduced lung and nasal viral titers in a dose-dependent manner. Protection in the lower respiratory tract upon challenge with RSV A and B was greater with RSM01 compared to palivizumab.

In summary, there were no test-article related target organ toxicities, no effects on vital systems, and no adverse local reactions reported in non-clinical safety studies. RSM01 demonstrated a favorable efficacy and safety profile supporting its progression for clinical development to prevent RSV disease.

2.4. Study Rationale

The burden of RSV infection, especially among infants and young children underscores the need for safe and effective prevention against RSV disease that is affordable in LMICs. The goal of the clinical development program for RSM01 is to develop a safe, effective, affordable mAb to prevent severe RSV disease in infants in LMICs. The clinical development approach for RSM01 is to first study a wide dose range in healthy adults to assess safety and to cover target exposures in infants that will allow for pharmacokinetic (PK)/pharmacodynamic (PD) modeling to provide confidence in predicting efficacious doses in infants.

Refer to Section 2.5 for justification of dose levels.

2.5. Justification for Dose

2.5.1. Doses for Escalation Phase Cohorts

The selection of the dosing strategy for dose escalation is based on non-clinical safety data and in vivo pharmacological evaluation in the cotton rat RSV prophylactic model. This approach is

supported by assessments of the PK profile of other RSV mAbs with YTE mutations. The wide dose range, from 300mg to 3000mg, in healthy adults would cover target exposures in infants and support PK/PD modeling to predict infant dosing.

RSM01 and nirsevimab were evaluated in the RSV cotton rat model. Collectively, the conclusion from those experiments is that the EC90s for RSM01 is similar to nirsevimab in term of PK/lung RSV titers. In the literature, nirsevimab has been reported to have a EC90 of 6.8 µg/mL [Zhu 2017].

The human PK exposure of RSM01 in healthy participants was projected based on extrapolation made from the non-human primate PK in the toxicology studies and published reports of the PK characteristics of competitor monoclonal antibodies (nirsevimab and MK-1654) in healthy volunteers.

These projections suggest that following RSM01 doses of ≥ 300 mg the RSM01 concentration is predicted to be above the target EC90 threshold at Day 151.

RSM01 was well-tolerated in a definitive study in monkeys with a NOAEL of 300 mg/kg/dose or 100 mg/dose following IV or IM administration, respectively. The NOAEL at 300 mg/kg, IV, provided safety margins of approximately 10-fold and 1.1-fold to the starting dose of 300 mg IV and ending dose of 3000 mg IV, respectively, based on predicted human AUC. There were no test-article-related local reactions following administration of 100 mg/mL of RSM01 by IM injection in monkeys, which supports dosing of 600 mg, IM in humans at 100 mg/mL of RSM01.

Safety and PK data from the FiH study in adults are required to support proceeding to the target population of infants. The wide fixed-dose ranges to be tested in healthy adults will cover the anticipated target exposures in infants. The 300 mg dose in adults is estimated to correspond to the target dose of 50 mg in infants. Importantly, the maximum dose for the escalation cohorts (3000 mg IV) and the maximum dose for the Expansion Phase cohort (600mg IM) will provide necessary safety information to inform selection of doses in infants.

2.5.2. Dose for Expansion Phase Cohort

Final selection of the dose to be administered to Cohort 5 will be made by the sponsor and informed by available RSM01 PK data, as well as relevant safety data, from the Dose Escalation Phase.

Available interim PK data from the Dose Escalation Phase cohorts, combined with published data from previous studies of monoclonal antibodies, will be used to develop a population PK model to describe the individual concentration time profiles of RSM01. Subsequently, the model will be used in a simulation mode to predict the proportion of participants that are expected to have RSM01 concentrations above the EC90 on Day 151.

The tentatively determined dose to be tested in the Dose Expansion Phase cohort is ≥300 mg and ≤600 mg IM, based on available pre-clinical and clinical PK data from nirsevimab and MK-1654 (Griffin 2017, Aliprantis 2020). The 600mg IM dose in adults is expected to provide additional margin for meeting the EC90 threshold at Day 151, even in the case that the t1/2 of RSM01 is shorter than those of nirsevimab and MK-1654. It will also provide additional information for infant dose selection for the planned Phase 1b/2a study.

The 600 mg IM dose is anticipated to be equivalent to the maximum possible infant dose of 100mg IM (based primarily on the IM volume constraint of 1mL).

2.6. Benefit/Risk Assessment

The non-clinical safety of RSM01 has been evaluated in GLP-compliant studies in monkeys of up to 4 weeks in duration. RSM01 was well-tolerated at all doses tested; there were no test-article related target organ toxicities, no effects on vital systems, and no adverse local reactions. Juvenile monkeys are commonly used in toxicology studies including studies conducted with RSM01. A tissue cross-reactivity study with biotinylated RSM01 found no risk for off-target binding of RSM01 in human tissues.

Clinical risks and benefits have not been established for RSM01 when administered to humans. However, it is expected that RSM01 will have a similar benefit/risk profile to nirsevimab.

There have not been safety concerns identified to date from the 3 clinical trials of nirsevimab that had 102 adults and 1039 infants exposed to nirsevimab. No SAE related to the compound occurred during these studies. A Phase 1 FiH study in adults in the U.S. evaluated a single dose of nirsevimab or Placebo administered as an IV dose of 300mg, 1000mg, or 3000mg or as an IM dose of 100mg or 300mg [Griffin, 2017] and did not have any study discontinuations due to AEs or SAEs. The most frequently reported nirsevimab-related AEs were headaches (all mild), occurring in 3 (2.9%) participants. The safety profile was similar to that of the Placebo.

In the second clinical trial, a Phase 1b/2a study evaluated a single IM dose of 10mg, 25mg or 50mg of nirsevimab or Placebo in infants in the U.S., South Africa, and Chile [Domachowske, 2018]. Five infants (7.0%) who received nirsevimab experienced product-related AEs, which included nasal congestion, pyrexia, gastroenteritis, upper respiratory tract infection and wheezing (all Grade 1), and 5 experienced medically-attended LRTIs through Day 150; 1 tested positive for RSV (10mg group).

In the third clinical trial, a Phase 2b study evaluated a single dose of 50mg IM of nirsevimab vs. Placebo in 1453 healthy preterm infants (29-34 weeks gestational age, aged 0-12 months). Through Day 150 of follow-up, AEs occurred at similar frequencies between the mAb (804/968, 83%) vs. the Placebo (402/479, 83.9%) groups. SAEs were reported in 108/968 (11.1%) mAb vs. 81/479 (16.9%) Placebo recipients, and none were considered related to study drug. AESIs related to study drug were reported in 5/968 (0.5%) in nirsevimab vs. 3/484 (0.6%) in Placebo. There were no anaphylaxis or other notable hypersensitivity reactions. In the nirsevimab group, 4 infants experienced rash. One infant experienced one day of petechiae occurring 4 months after nirsevimab, which was not assessed by a health care provider. All 3 AESI infants in the Placebo group had rash.

AEs attributed to ADAs have not been observed in the nirsevimab trials. In the Phase 1 adult trial, ADA occurred at a similar frequency in the mAb and Placebo groups. At the baseline visit, 5/103 (4.9%) mAb vs. 3/34 (8.8%) Placebo recipients had ADA. During post-dose visits, 14/102 (13.7%) mAb vs. 5/33 (15.2%) Placebo recipients had ADA. In the nirsevimab Phase 1b/2a infant trial none had ADA at baseline and only the mAb group had ADA at post baseline (20/71, 28.2%) vs. 0/17 in the Placebo group. Aside from 2 infants with transient positive ADA at day 50, all positive ADAs occurred after the intended coverage duration of 150 days. ADA did not impact safety but lowered the drug exposure between days 150 to 360 in some infants.

The Phase 1 MK-1654 study randomized 152 healthy adults in a 3:1 ratio to MK-1654 (100mg IM, 300mg IM, 300mg IV, 1000mg IV and 3000mg IV) vs. Placebo. The overall safety profile of MK-1654 was similar to that of Placebo. No deaths, SAEs, discontinuations due to AEs, clinically significant laboratory AEs, or dose-dependent pattern of drug-related AEs were reported [Aliprantis 2020].

RSV Mutations

RSV belongs to the class of ribonucleic acid (RNA) viruses and as such possesses an error-prone RNA polymerase. This raises potential concerns about the emergence of antibody resistant escape mutants. This is especially relevant for mAb that are considered for wide-spread use and target a single epitope on the viral surface. Zhu, et al published data on RSV escape variants against nirsevimab, a highly potent, next generation anti-RSV-F antibody that also binds to antigenic site Ø that is currently under clinical investigation [Zhu 2018].

Escape mutant selection studies with RSM01 were performed by the former sponsor, Arsanis (Vienna, Austria). A total of 11 escape mutant selection studies were conducted by Arsanis during the selection phase of RSM01. Although previously identified antibody resistant mutants against palivizumab and nirsevimab were obtained, not a single resistance associated mutation was identified for RSM01, parental mAb 15618, or additional 15618 variants. The data suggest that the epitope of RSM01 is more stable and less prone to amino acid substitutions under selective pressure compared to nirsevimab. This is interesting since RSM01 and nirsevimab bind to the same antigenic site (epitopes differ) on the F protein and have largely comparable neutralization potency based on in vitro and in vivo virus neutralization assays. RSM01 maintained anti-viral activity against a nirsevimab resistant strain, RSV-B9320 N208D [Rouha 2018].

In vitro cell-based neutralization studies showed that RSM01 performed better than other RSV monoclonal antibodies palivizumab and REGN222 to neutralize both RSV A and RSV B strains including important sequence variants. RSM01 potency was comparable to that of nirsevimab.

General Risks with MAb Infusion

Administration of any mAb may carry a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies against the mAb. However, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine monoclonal antibodies, which would have a risk of human anti-mouse antibodies. In this regard, as RSM01 is targeted to a viral antigen, is a fully human mAb (IgG1), and is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild but may include fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain.

Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia, are infrequent and more often associated with mAbs targeted to human proteins and not pathogen-directed human mAbs like RSM01. Immediate infusion reaction is managed by temporarily stopping the infusion, administration of histamine blockers and restarting the infusion at a slower rate [Vogel 2010]. Delayed allergic reactions to a mAb may include a serum

sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the mAb and are noted to be more common with non-human/human chimeric types of mAbs [Hansel 2010]. Antibodies containing the YTE mutations in the Fc region have been safe and well-tolerated in humans [Robbie 2013, Aliprantis 2020, Griffin 2020].

No direct benefits are anticipated for the healthy adults enrolled in this Phase 1 study. RSM01is expected to have favorable safety profile based on experience with other fully human monoclonal antibodies targeting various viruses (e.g., anti-HIV, anti-influenza, and anti-RSV).

3. Objectives and Endpoints

Table 4: Objectives and Endpoints

Objectives	**Endpoints** *(Endpoints apply to all cohorts unless noted)*
Primary	
To characterize the safety and tolerability of a single dose of RSM01	• Unsolicited AEs through Day 151 • All serious adverse events (SAEs) and AESIs through Day 151 • Solicited systemic AEs for 7 days after dose administration • Solicited local AEs for injection site reactions for 7 days after dose administration (only applies to IM doses)
Secondary	
To characterize safety laboratory parameters following RSM01 administration	• Safety laboratory parameters Grade 1 and above 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 ($AUC_{0-\infty}$) • Day 91 capillary blood-concentration and area under the capillary blood-concentration time curve (C_{D91} and AUC_{0-D91}) • Day 151 capillary blood-concentration and area under the capillary blood-concentration time curve (C_{D151} and AUC_{0-D151}) • C_{max} following IM administration and C_0 following IV administration), C_{min} • T_{max} and t1/2 • CL • Vz of RSM01 through Day 151
To characterize the formation of ADAs following RSM01 administration	• Incidence of ADAs to RSM01 through Day 151

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

4. Study Design

4.1. Design Overview

Overall Design

Disclosure statement: This is a FiH trial of RSM01, administered to adults. It is a randomized, double-blind, placebo-controlled study of RSM01.

Study Population and Number of Participants: Adult participants between 18 and 49 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent may be eligible for the study. The complete list of inclusion and exclusion criteria can be found in Section 5.1and Section 5.2, respectively.

Candidates will be screened to enroll 56 eligible participants.

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

Interventional model*:* 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.

Dose Escalation Phase:

The first participant in each Dose Escalation Phase cohort will not be randomized and will receive the RSM01 dose level appropriate to assigned cohort to serve as a sentinel exposure (refer to Section 8.1.1).

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 occur sequentially in 2 escalation steps.

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

First escalation step: from Cohort 1 to Cohorts 2 and 3, conducted in parallel

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

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

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

For the Dose Escalation Phase cohorts, all participants will be confined at the study site from Day -1 (i.e., the day before dosing) to after completion of the Day 3 assessments (a total of 3 nights).

Dose Escalation Phase, continued:

After the sentinel participant in each cohort receives RSM01, the next participant can be dosed 24 hours later, if there is no safety concern.

After the 24-hour post-dose period for the sentinel participant in each Dose Escalation Phase cohort, participants in the Dose Escalation Phase cohorts should be dosed at least 2 hours apart regardless of route of administration (IM or IV). The ≥2-hour interval between administering IV infusions is to begin at the end of the previous infusion.

For participants receiving the IM dose of study drug in Cohort 2, the ≥2-hour interval between administering IM injections to successive participants is to begin at the time of the previous participant's IM injection. If RSM01 is administered using 2 injections, the ≥2-hour interval begins at the time of the second injection.

Each dose escalation step will proceed after all participants the prior cohort have completed Day 15, and the SRT has reviewed the data and determined that a pausing rule has not been met. Refer to Section 8.2.6 for details regarding the SRT.

Dose Expansion Phase:

Enrollment in the Dose Expansion Phase (Cohort 5) will begin after Day 15 for participants in Cohort 4, and after the SRT has reviewed the data and determined that a pausing rule has not been met. Cohort 5 will include 28 participants randomized 6:1.

- Cohort 5: participants will receive RSM01 IM (n=24) or Placebo IM (n=4).

For Cohort 5, participants will be asked to present to the clinic within 24 hours of the Day 1 visit for Day -1 (Pre-V1) confinement.

On Day 1 after dosing, participants will be observed for at least 4 hours post-dose at the study site for safety monitoring. Based on investigator's decision, a participant may be asked to remain at the study site, for an additional overnight stay on the night of Day 1.

Final selection of the dose of RSM01 to be administered to Cohort 5 will be made by the sponsor and informed by available RSM01 PK data from the Dose Escalation Phase.

The tentatively determined dose to be evaluated in the Expansion Phase cohort is ≥300 mg to ≤600 mg IM. This determination is based on predictions of RSM01 human PK exposures made using extrapolation from the RSM01 non-human primate PK and on published data from the other mAbs nirsevimab and MK-1654 administered to healthy adults [Griffin 2017, Aliprantis 2020]. The predictions suggest that the concentration of RSM01 will be above the efficacy threshold (EC90) on Day 151 following a RSM01dose of either 300 or 600 mg IM. Refer to Section 2.5.2 for dose justification.

Pausing rules: Refer to Section 7.1.1

SRT and IDMC: Refer to Sections 8.2.6 and 8.2.7 for information regarding the SRT and IDMC, respectively.

Visits: The study Schema is shown in Figure 1: Outline of Study Dosing Procedures and the SoA is shown in Table 2 and Table 3, Dose Escalation Phase and Dose Expansion Phase, respectively.

Blood Sampling: Refer to Section 8.4.

Masking: Refer to Section 6.5.2.

Analyses: An interim analysis will occur after all participants in the Dose Escalation Phase cohorts 1-4 have reached Day 91. The primary analysis will occur after all participants in all 5 cohorts complete Day 151. Refer to Section 9.

Total duration of study participation: The study duration for each participant is 151 days, in addition to a maximum 30 days for screening and Day -1.

Study site/s: The study will be conducted in at least 1 site in the U.S.

4.2. End of Study Definition

A participant is considered to have completed the study if he/she completes the final visit at Day 151.

The end of the study is defined as the date of the last visit of the last participant in the study or conduct of the last scheduled procedure shown in the SoA for the last participant in the trial.

5. Study Population

A total of 56 eligible, healthy adult participants between 18 and 49 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent will be eligible for the study. See Section 5.1 and 5.2 for inclusion and exclusion criteria, respectively. Candidates will be screened for eligibility to enroll.

Prospective approval of deviations to recruitment and protocol enrollment criteria, also known as protocol waivers or exemptions, will not be permitted.

Recruitment

All recruitment materials will be approved by the appropriate Institutional Review Board/s (IRBs) or Independent Ethics Committee/s (IECs). Interested participants will be invited to participate in the informed consent process.

Various methods of recruitment may be used, such as site databases, advertising, referrals, word-of mouth, or other approved means.

5.1. Inclusion Criteria

Age

1. Participant must be 18 to 49 years of age (inclusive) at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation including medical history, physical examination, and laboratory tests

Weight

3. Body mass index (BMI) 18 to 29.9 kg/m^2 (inclusive)

Sex

4. Both males and females are eligible to participate.

   Male participants with partners of childbearing potential must agree to use condoms during their participation in the study and for 90 days after the participant completes the study. Male participants must also agree to refrain from sperm donation for at least 90 days after they complete the study.

   Female participants of childbearing potential must not be pregnant, breastfeeding, or attempting to become pregnant for 28 days before Screening and throughout the duration of their participation in the study. These participants must have a negative serum pregnancy test at Screening in order to be eligible for randomization and treatment with study intervention. In addition, female participants must be willing to commit to using a consistent and acceptable method of contraception for the duration of their participation in the study and for 90 days after they complete the study if they engage in intercourse. Acceptable methods of contraception are:

   - Consistent use of systemic contraception, including birth control pills, transdermal patch, vaginal ring, implants, and injectables.
   - Consistent use of double barrier method, e.g., condoms, cervical cap, diaphragm, vaginal contraceptive film with spermicide.
   - Use of intrauterine device with a low failure rate (defined as < 1% risk of pregnancy per year)
   - Monogamous intercourse with a vasectomized man or has only same-sex partners.

   Female participants who are not sexually active but become so during the study must agree to follow the contraceptive requirements above.

   Female participants who are not of childbearing potential must meet at least one of the following criteria:

   - At least 1 year since the last menstrual period.
   - Surgically sterile (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy)
   - Congenitally sterile

- Diagnosed as infertile and not undergoing treatment to reverse infertility.

Refer to Appendix 10.3 for more information.

Informed Consent

5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

Additional Requirements:

6. Participants must agree to stay in contact with the study site for the duration of the study, provide updated contact information as necessary, and have no current plans to relocate from the study area for the duration of the study.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Acute illness and/or body temperature ≥37.5°C or ≥99.5°F on Study Day 1 (refer to Section 5.4 for additional details). NOTE: This is a temporary exclusion for which the participant may be re-evaluated.
2. Evidence and/or history of clinically significant medical condition(s) as judged by the investigator, including malignancies, diabetes mellitus, and unstable or uncontrolled hypertension
3. History of any autoimmune disease or immune deficiency or other impairment to the immune system, including but not limited to HIV, autoimmune conditions, or immunosuppressive therapy. Note: history of Hashimoto's thyroiditis is not an exclusion criterion.
4. History of anaphylaxis
5. Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the investigator, will make it unlikely that the participant will comply with the protocol

Prior/Concomitant Therapy

6. Receiving or plan to receive any medications or other therapies that may impact the immune system such as allergy injections, interferon, immunomodulators, cytotoxic drugs or other drugs known to be frequently associated with major organ toxicity within 90 days prior to Day 1.
7. Having received any vaccination (including COVID-19 vaccine) within the 15 days before Day 1, or planning to receive a dose of any vaccine during the 15-day period following Day 1.
8. Receiving or plan to receive immunosuppressive agents including systemic steroids within 90 days prior to Day 1 (individuals using inhaled or topical corticosteroids, prednisone (or equivalent) dose of ≤ 20 mg/day for ≤ 14 days, and intra-articular corticosteroids are permitted)

9. Receipt or donation of blood or blood products within 90 days prior to Day 1 or planned receipt or donation during the study period
10. Receiving or plan to receive antibody or biologic therapy within 180 days prior to Day 1 or any time during the study period, whether licensed or investigational (e.g., immunoglobulin products, monoclonal antibodies, or antibody fragments).

Prior/Concurrent Clinical Study Experience

11. Participation in an interventional clinical trial and/or receipt of any investigational drug within 30 days or 5 half-lives of the investigational drug before the first day of study drug dosing in this study, whichever is longer
12. Concurrent enrollment in another interventional study
13. Previously having participated and received study intervention in the current study.

Diagnostic Assessments

14. Female participants: positive serum pregnancy test
15. Safety laboratory values outside of normal range, for age and sex that are suggestive of a disease state (Grade 1 abnormalities will not lead to exclusion if the investigator considers them not clinically significant.)
16. Urinalysis abnormality greater than Grade 1 (with the exception of hematuria in a menstruating female), or urinalysis abnormality judged clinically significant by the investigator
17. Clinically significant ECG abnormalities
18. Reactive HIV antibody testing
19. Current hepatitis B and/or hepatitis C infection
20. Positive urine drug screen at screening or Day-1 (with the exception of prescribed drugs).

Other Exclusions

21. History of allergy or hypersensitivity to the study drug, excipients or related substances
22. Female participants with any one of the following conditions: currently pregnant or lactating/nursing; having positive serum pregnancy test during the Screening Phase, planning a pregnancy within 1 year after first dose of study drug (Refer to Appendix 3, Section 10.3)
23. Individuals who are acting as study personnel or immediate family members (brother, sister, child, parent) or the spouse/partner of study personnel.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into the study and do not receive study intervention. A minimal set of screen failure information is required to ensure transparent reporting of criteria for participants who are screen failures in order to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria not met, and any SAE.

Rescreening assessments as outlined below may be performed after obtaining informed consent, which must be completed prior to any rescreening procedure.

Rescreening is only permitted under one or more of the following scenarios:

- If a participant presents with an acute illness on the day of planned study intervention, e.g., elevated temperature, acute respiratory or gastrointestinal illness, or urinary tract infection (UTI), and meets all other eligibility criteria and can be rescreened within the originally defined screening window (SoA, Section 1.3). A new participant number is not required. If the participant is rescreened during the original screening window, obtaining a second informed consent of the participant is not required.

- If there are technical difficulties with phlebotomy at screening (e.g., laboratory reports hemolyzed blood), technical error in running the laboratory tests or an abnormal urine analysis due to menstruation or UTI, and the participant can be rescreened within the originally defined screening window (SoA, Section 1.3). A new participant number is not required. If the participant is rescreened during the original screening window, obtaining a second informed consent of the participant is not required.

- If a participant is undergoing screening and the study reaches a pausing rule. The participant may be rescreen*ed* when and if the IDMC recommends, and the Sponsor determines, that the study may continue. A new participant number is not required. If the participant is rescreened during the original screening window, obtaining a second informed consent of the participant is not required.

- If a participant fails to meet eligibility criteria upon initial screening, a one-time only rescreening for eligibility may be performed. In this case, the participant must be given a new participant number after signing a new informed consent.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), Placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Two interventions will be used in this study: participants will receive either RSM01 or Placebo based on randomization as described in Study Design, Section 4.

Participants in the Dose Escalation Phase cohorts will receive a single dose of either 300mg IV, 1000mg IV, 3000mg IV or 300mg IM, of RSM01, or Placebo.

The Expansion Phase cohort will receive a single dose of RSM01 IM or Placebo. The RSM01 dose will be selected based on review of available PK data from prior cohorts, as well as relevant safety data.

Table 5: Study Interventions

	RSM01 Drug Product	**Placebo (Control)**
Intervention	RSM01 (RSV F neutralizing monoclonal antibody)	Matching formulation buffer without API RSM01
Unit-Dose Strength	100mg/mL	N/A
Dose Escalation Phase cohorts		
Dosage, Volume and Route of Administration	300mg (53mL) IV infusion 1000mg (60mL) IV infusion 3000mg (130mL) IV infusion 300mg (3 mL) IM injection (1 injection in the anterolateral thigh muscle)	Same volume and number of infusions/injections as the RSM01 group.
Dose Expansion Phase Cohort		
Dosage, Volume and Route of Administration	Dose to be determined. Route of administration will be IM in the anterolateral thigh muscle.	Same volume and number of injections as the RSM01 group.

6.1. RSM01 Drug Product

The RSM01 Drug Product (RSM01) used in this study is manufactured by Just-Evotec Biologics, Inc. RSM01 is supplied as a liquid in a single use, sterile filled glass vial at a product concentration of 100mg/mL, and 100mg/vial configuration. The volume injected or infused will vary depending on the cohort.

Each vial contains an isotonic, sterile solution that is a colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. Refer to Pharmacy manual for details.

6.2. Placebo Drug Product

The RSM01 Placebo Drug Product (Placebo) control consists of all the excipients without the mAb, in the same type of vial/cap/seal fill as the RSM01 presentation. The volume injected or infused will depend on the randomized group and will be the same as the volume of the RSM01 administered to participants within each respective cohort.

Each vial contains an isotonic, sterile solution that is a colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. Refer to Pharmacy manual for details.

6.3. Study Intervention Preparation and Administration

Refer to Section 4.1 for dose administration within each cohort and Section 6.4 for handling, storage, and accountability.

Unit-dose syringes will be provided for IM administration, and infusion bags for IV administration, all of which will be identified with the participant identification number, date and time of dose preparation, and the volume prepared. An investigator (i.e., physician) must be present in the clinic at the time of administration of the study interventions.

Visually, RSM01 is transparent and the appearance is comparable to that of the Placebo.

The Placebo control will be administered in the same manner as the RSM01, within each cohort.

IM administration into the anterolateral thigh muscle will be performed using standard ’Z-track’ technique. Refer to Section 6.3.1.

IV infusion will be administered over a duration of up to 2 hours using a volumetric pump. The infusion rate may vary based on the total volume needed to administer the full dose. The total time needed to administer the dose may be longer than 2 hours based on factors such as participant tolerance. Refer to Section 6.3.2.

For the Dose Escalation Phase, the first (sentinel) participant undergoing study intervention administration in each cohort will receive RSM01. The next participant in each cohort can be dosed at least 24 hours after the sentinel participant. After the 24-hour post-dose period for the sentinel participant in each Dose Escalation Phase cohort, participants in the Dose Escalation Phase should be dosed at least 2 hours apart regardless of route of administration (IM or IV). The ≥2-hour wait time between IV infusions is to begin at the end of the previous participant’s infusion. The ≥2-hour wait time between IM injections is to begin at the time of the previous participant’s IM injection.

For the Dose Expansion Phase, participants will be observed either overnight or for at least 4 hours at the study site after receiving the study dose, depending on the investigator’s decision.

6.3.1. IM Injection

Before administering the injection, the study intervention administrator must inspect the syringe and vial volume, checking that the syringe is identified with the correct participant identification

number and checking the date and time the dose was prepared. For IM dosing in the Dose Escalation Phase, participants in Cohort 2 will receive a total of 3mL administered in 1 injection into the anterolateral thigh muscle at the dosing visit, using the 'Z-track' technique. The ≥2-hour wait time between administration of IM injections to successive participants is to begin at the time of the previous participant's injection.

The Dose Expansion Phase cohort may receive RSM01 (≥300mg to ≤600mg) or Placebo in the anterolateral thigh muscle. If more than 3 mL of study intervention is administered in a single dose, the volume and number of injections will be adapted, depending on the dose to be administered, and will be decided by the sponsor.

6.3.2. IV Infusion

The formulation for RSM01 is 100mg/mL, and the appropriate volume, based on group randomization, will be added to normal saline to achieve the desired volume for each of the IV-dosed cohorts. The total IV infusion volume will be 53mL for Cohort 1, 60 mL for Cohort 3, and 130mL for cohort 4. The IV infusion time will be approximately 2 hours or less depending on the cohort. The ≥2-hour wait time between administration of IV infusions to successive participants is to begin at the end of the previous participant's infusion.

6.4. Handling/Storage/Accountability

Further guidance and information for the preparation, handling, storage, and accountability are provided in the Pharmacy Manual.

The study intervention (RSM01 and Placebo) must be stored at 2°C to 8°C in a secure location with no access for unauthorized personnel.

The study pharmacist (or designee) must confirm appropriate temperature conditions have been maintained during transit and during site storage for all study interventions received and any discrepancies are reported and resolved before use of the study intervention. Upon receipt of study supplies, the study pharmacist must immediately inspect all kits for damage. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor and the study monitor to determine the appropriate action.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Authorization for any unused study intervention and supplies to be destroyed is the responsibility of the sponsor. At the end of the study, unused supplies will be destroyed according to the facility's Standard Operational Procedures (SOPs) or per local regulations. Any disposal of study intervention conducted at the clinical site must be documented in the study file.

6.5. Measures to Minimize Bias: Randomization and Blinding

6.5.1. Randomization

The first participant in each Dose Escalation Phase cohort will not be randomized and will receive RSM01 dose level appropriate to the assigned cohort (refer to Section 8.1.1).

The remaining 6 participants in each Dose Escalation Phase cohort (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 Expansion Phase (Cohort 5) will be randomized 6:1 to receive either RSM01 IM (N=24) or Placebo (N=4).

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

Before the study is initiated, the telephone number and call-in directions for the Interactive Voice response system and/or the log in information and instructions for the Interactive web response system will be provided to the study sites.

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.

Randomization for each participant will take place on Day 1.

6.5.2. Masking

The study is double-blind: participants and all study personnel will be blinded to the randomization, with one exception: the first sentinel participant in each Dose Escalation Phase cohort will be single-blinded (participant-blinded) and receive the respective dose of RSM01. Authorized study site personnel will administer doses.

The unblinded investigational pharmacist will provide the prepared doses of RSM01 and Placebo to the clinic appropriately masked to the blinded treating nurse/physician.

Only the following personnel will have access to the treatment allocation while the study remains blinded to other personnel:

- Pharmacist preparing the RSM01 and Placebo doses
- Biostatistician preparing the randomization list
- Biostatistician preparing the IDMC data, as applicable, and for the interim analysis
- Pharmacometrician preparing the PK data for IDMC (as applicable) and for the interim analysis
- IDMC members, as applicable
- Unblinded study Monitors.

Additionally, the supplies manager/designate and quality assurance personnel of the sponsor, as well as the IXRS system setup person and PK simulation and modeling vendor will have access to unblinding information.

All unblinded persons must take care to not reveal individual group assignments to any other member of the study team.

Any study staff that become inadvertently unblinded must not participate in the evaluation of AEs. A delegation of authority log will be maintained by the site and will identify the individual(s) authorized to function as individuals with access to study blinding information.

The interim analysis will be performed by an unblinded statistician. The investigator will be blinded during the entire study.

Blinding will be maintained during the aggregated PK data review to select the Dose Expansion Phase cohort dose and during interim analysis.

The sponsor will review aggregated safety data by cohort only (data from both RSM01 and Placebo participants will be included) and will review aggregated PK data by treatment group (RSM01 vs. Placebo) within and across cohorts for the following purposes: *1)* selecting dosing for the Dose Expansion Phase cohort, and *2)* reviewing the interim analysis to inform a decision and plan for the infant study. Although the sponsor will be blinded throughout the study, such review of aggregated data could potentially lead to individual unblinding. An unblinding plan will be prepared to include unblinding details.

6.5.3. Blind Break

The IXRS will be programmed with blind-breaking instructions. In addition, instructions on emergency unblinding in case of system outage will be provided. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded at any time during the study, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

6.6. Study Intervention Compliance

Participant compliance with study intervention will be recorded on his/her CRF.

6.7. Concomitant Therapy

Any prescription medication, anti-inflammatory drug, antipyretic drug, or vaccine that the participant receives from enrollment through study Day 151 must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A COVID-19 vaccination may be received by a participant during the study but not within the 15 days immediately following administration of the study intervention.

6.8. Dose Modification

No unplanned dose modifications are allowed. This is a dose escalation and dose expansion study. Refer to Section 3 for details regarding dose escalation and dose expansion.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

A participant withdrawn from the study intervention (i.e., any participant who does not receive the study intervention) will be withdrawn from the study.

7.1.1. Pausing Rules

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 toxicity 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 and the U.S. FDA will be notified in an expedited manner.

Refer to Section 8.2.6 for the role of SRT and Section 8.2.7 for the role of the IDMC.

If the investigator and/or the SRT observes that a pausing rule is met, the investigator will inform the sponsor and/or the SRT as soon as possible and within 24 hours of the observation. The SRT and/or sponsor will notify the investigator and the IDMC members of the pause in enrollment and participant dosing as soon as possible and within 24 hours of receiving notification of the pausing rule being met.

When a pausing rule is met, the IDMC members will convene an urgent ad hoc review meeting, review all relevant unblinded safety data, and make a recommendation to the sponsor. The FDA will be advised of the IDMC actions and recommendations.

The IDMC may recommend continuation of the study pause or resumption of enrollment and dosing with or without changes to the protocol. The final decision to pause or resume study activities will always be the responsibility of the sponsor. All IDMC recommendations will be stored according to the IDMC Charter.

All sponsor decisions will be documented in a memorandum to the study file. The sponsor or delegate is responsible for prompt communication to the study site of decisions related to pausing or resuming the study activities, including notification to the investigator, relevant IRBs/IECs and regulatory authorities.

The clinical site will be allowed to resume activities only upon receipt of written notification from the sponsor.

7.2. Participant Discontinuation or Withdrawal from the Study

A participant may request withdrawal from the study at any time. A participant may also be withdrawn from the study at any time for the following reasons:

a. at the request of the primary care provider if being in the study is no longer in the best interest of the participant

b. participant is judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results

c. at the discretion of the IRB/IEC or government agencies as part of their duties, investigator, or sponsor.

If possible, a discontinuation visit should be scheduled for any participant who wishes to discontinue or withdraw from the study. At this visit, topics around participant safety as well as the use of already collected biospecimens will be discussed, and the procedures and specimen collection indicated in the SoA (Table 2 and Table 3) will be performed if possible and as needed.

The time and reason for withdrawal should be noted in the space provided for this purpose in the CRF. Possible reasons responsible for withdrawal include:

- no receipt of study intervention
- SAE
- non-serious AE
- protocol violation (specify)
- consent withdrawal not due to an AE*
- move from study area
- other (specify).

*If a participant withdraws consent, the reason, if specified, will be documented in the CRF.

Participants who are withdrawn because of occurrence of AE should be clearly distinguished from participants who are withdrawn for other reasons. Participants who are withdrawn because of an AE will be followed until the event resolves or stabilizes.

Refer to Appendix 1, Section 10.1.4 regarding the informed consent process.

All data collected until the date of withdrawal/last contact of the participant will be used for the analysis, unless the participant requests destruction of any samples taken and not tested. The investigator must document this in the site study records and the CRF. If the participant withdraws consent for disclosure of future information the sponsor may retain and continue to use any data collected before such withdrawal of consent.

If the participant leaves the study, the participant's medical information will still be used or shared to the extent allowed by law. Any leftover samples will be destroyed after testing is completed unless the participant withdraws consent to sample use, in which case the samples will be destroyed at that time. Any test results from the samples collected before withdrawal can still be included in the analyses.

A participant who becomes pregnant during the study period will be asked to complete all visits and procedures through Day 151 as described in Table 2 or Table 3, as applicable. After she

completes Day 151, or in the event that she voluntarily withdraws from the study and agrees to provide additional information regarding the pregnancy, the investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate. Neonate follow-up will occur for 6 weeks beyond the estimated delivery date (refer to Section 10.3).

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (3 failed visits) and is unable to be contacted by the study site (3 failed attempts per failed visit).

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a home visit by a member of the study team). These contact attempts should be documented in the participant's medical record and the CRF.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up from the study.

7.4. COVID-19 Contingency Plans

In the event that SARS-CoV-2 coronavirus disease (COVID-19) affects the conduct of this trial, the sponsor will evaluate if in-person visits are necessary to fully ensure the safety of trial participants and whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment such as local laboratories or home visits) could be implemented when necessary and feasible, and would be sufficient to ensure data integrity and safety of participants [FDA, 2020].

Any contingency plans must be sufficient to ensure the safety of trial participants. Changes in study visit schedules, missed visits, or withdrawal of the study intervention or participant discontinuations may lead to missing information (e.g., for protocol-specified procedures) must be captured in the CRF that explains the basis of the missing data (i.e., COVID-19).

Approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at the study site must be documented. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations.

Deviations because of COVID-19 will be described in the clinical study report or in a separate study-specific document) including but not limited to the following:

- Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
- A listing of all participants affected by the COVID-19 related study disruption by unique participant number identifier and by investigational site, and a description of how the individual's participation was altered.
- Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the results reported for the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Adherence to the study protocol, including those specified in the SoA, is essential and required for study conduct.

Prior to any study procedure, all eligible participants will be assigned a unique participant identifier. This participant identifier will be used throughout the study for participant identification.

Screening for eligibility assessment will occur after informed consent is obtained. Eligibility for randomization will be based on the inclusion and exclusion criteria described in Section 5.1 and Section 5.2, respectively.

Eligibility criteria will be checked during the screening process and prior to RSM01 or Placebo administration to ensure that all participants enrolled meet all of the inclusion criteria and none of the exclusion criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record the reasons for screening failure, as applicable.

To evaluate eligibility criteria, a medical history and physical examination including vital signs will be performed.

In addition, safety laboratory tests (hematology, chemistry, and urinalysis), HIV, hepatitis B and C screening, urine drug test, 12-lead ECG, and serum pregnancy test (females only) will be performed.

The investigator must document confirmation of eligibility prior to randomization.

8.1. Safety Assessments

The screening visit will take place between 30 days and 2 days before the planned Day 1 visit.

All participants will also be required to attend the Day -1 (Pre-V1) visit within 24 hours before planned dosing to begin confinement.

A negative serum pregnancy test (based on the serum sample collected on Day -1) must be confirmed prior to study intervention administration on Day 1.

All Day 1 safety assessments and sample collections are prior to administration of study intervention.

Prior to opening Cohorts 2 and 3 together, Cohort 4, and Cohort 5, respectively, to enrollment, the SRT will conduct safety assessment of data for the previous cohort/s collected when all participants in the currently dosed cohort have completed Day 15.

During each IV infusion, any infusion reactions will be recorded.

Planned time points for all safety assessments are provided in the SoA.

8.1.1. Confinement Period and Sentinel Participants

Details regarding confinement period are provided in the study manual.

Dose Escalation Phase

Participants in the Dose Escalation Phase will be confined at the study site from Day -1 to after completion of Day 3 assessment (a total of 3 nights).

On Day -1, participants will undergo safety laboratory assessments and other screening procedures (refer to the SoA, Table 2).

The first participant in each of the Dose Escalation Phase cohorts will be a sentinel participant and will receive RSM01 at the respective dose of RSM01 in a participant-blind fashion.

The next participant in each cohort can be dosed at least 24 hours later, if there is no safety concern.

Dose Expansion Phase

For the Expansion Phase, participants will be asked to present to the clinic within 24 hours of the Day 1 visit. On this Day -1 visit, participants will begin confinement, and undergo safety laboratory assessments and other screening procedures (refer to the SoA, Table 3).

On Day 1 after dosing, participants will be observed for at least 4 hours post-dose at the study site for safety monitoring, and based on investigator's decision, a participant may be asked to remain for an additional overnight stay on the night of Day 1.

8.1.2. Full Physical Examination and Medical History

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

All conditions that exist prior to administration of study intervention will be recorded in the medical history. Day-to-day fluctuations in these conditions that do not represent a clinically significant change in the participant's status will not necessarily be reported as AEs.

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).

8.1.2.1. Vital Signs

Vital signs will be taken at screening and on Day 1, prior to RSM01/Placebo administration.

Vital sign measurements will be recorded for pulse rate, systolic and diastolic blood pressure, respiratory rate, body temperature and percent oxygen saturation by fingertip pulse oximetry. Vital signs are to be taken after the participant is seated for at least 5 minutes in a quiet setting without distractions. Measurements are to be repeated if clinically significant changes are observed or a machine error occurs.

Vital signs for the Dose Escalation Phase:

- On Day 1 vital signs will be taken pre-dose, and 1 hour, 4 hours and 8 hours after the IM dose and at pre-dose, 15, 30 and 45 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, and 8 hours after the IV dose. The window for these measurements is ± 3 minutes.
- 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 Visit vital signs will be taken at 48 hours after dosing. The window for these measurements is ± 1.0 hours.

Vital signs for the Dose Expansion Phase:

On Day 1, vital signs will be taken pre-dose and 4 hours post-dose. The window for these measurements is ± 3 minutes. If the participant stays overnight on Day 1, vital signs will be taken at 24 hours after dosing. The window for these measurements is ± 0.5 hours.

8.1.3. Focused Physical Examination and Medications/Vaccinations

Focused physical examinations, will be performed on Day 1 and all subsequent visits, as indicated in the SoA (Table 2 and Table 3).

A focused physical examination will be performed 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.

Throughout the study, any concomitant medications taken, including antipyretics, anti-inflammatories, and vaccinations will be recorded (refer to Section 6.7).

8.1.4. Pregnancy Status Assessment

A blood sample will be collected from female participants at screening and at Day -1 for serum beta human chorionic gonadotropin (βHCG) testing.

Serum βHCG testing of female participants should be performed during the study if a pregnancy is suspected.

Serum βHCG testing of female participants of childbearing potential should be performed at the discontinuation visit.

During the study, participants will be asked about pregnancy during each visit. If a pregnancy is reported, the investigator should inform the Medical Monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3, Section 10.3.

A participant who becomes pregnant during the study period will be asked to complete all visits and procedures through Day 151 as described in Table 2 or Table 3, as applicable. After she completes Day 151, or in the event that she voluntarily withdraws from the study and agrees to provide additional information regarding the pregnancy, the investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate. Neonate follow-up will occur for 6 weeks beyond the estimated delivery date (refer to Section 10.3).

8.1.5. HIV Antibody Assessment

To be eligible for the study, participants must not have reactive anti-HIV antibody at screening. A blood sample will be collected to make this assessment.

8.1.6. Electrocardiogram, Hepatitis Screening and Urine Drug Screening

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. For the Dose Escalation Phase, the ECGs will be taken at screening, and 24 hours post-dose, on Day 2. For the Dose Expansion Phase, the ECGs will be taken at screening.

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.

At the screening visit, a blood sample will be collected to test for the presence of hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies.

A urine sample will be collected at screening and at Day -1 to screen for evidence of drugs of abuse.

8.1.7. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be performed at screening, on Day -1 (Pre-V1), and throughout the study at timepoints specified in the SoA (Section 1.3).

Blood samples for laboratory assessments will be collected at screening, and at study visits indicated in the SoA.

Laboratory values from the most recent blood sample collected prior to randomization that are outside the normal range that are suggestive of a disease state (i.e., clinically significant Grade 1 abnormalities or values greater than Grade 1 [refer to Section 10.4]) will lead to exclusion from study enrollment, with the exception of any grade hematuria in a menstruating female, or a urinalysis abnormality judged not clinically significant by the investigator.

Refer to Section 10.4 for toxicity table for grading for each clinical laboratory test.

Clinical safety laboratory parameters that will be evaluated include:

a. Hematology: Complete blood count (including hemoglobin, platelet count and white blood cell count) and absolute counts for neutrophils, lymphocytes, eosinophils, and monocytes

b. 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.

c. Urinalysis: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick.

Abnormal results and findings that make the participant ineligible for study participation will be discussed with the participant and the participant will be referred for follow-up care with their health care provider if necessary.

All screening laboratory specimens will be processed according to laboratory SOPs available from the clinical laboratory(ies) designated for the study.

All protocol-required safety laboratory tests will be performed by the site local laboratory or at the point of care. Laboratory safety testing performed at point of care will be documented in participant source and captured in the electronic data capture (EDC) database.

Information about the laboratory(ies), including any instructions for performing and interpreting specific tests, will be maintained in the investigator's study files.

The investigator must review the laboratory report, document the review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments require a change in participant management or are considered clinically significant by the investigator (e.g., AE or SAE), then the results must be recorded in the CRF.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

8.1.8. Pre- and Post-Study Intervention Safety Monitoring

Participants will remain under observation at the study site for 3 days in the Dose Escalation Phase cohorts (24 hours before dosing and 48 hours after dosing). Participants in the Dose Expansion Phase cohort will present to the study site before the planned Day 1 visit. After treatment on Day1, the participant will be observed for 4 hours at the study site and may remain overnight based on investigator's decision.

Allergic reactions to RSM01 are possible, therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a physician trained to recognize and treat anaphylaxis must be present in the clinic during study intervention administration and the post-dosing monitoring period.

8.1.9. Diary Card, Memory Aid and Daily Monitoring

Diary card

Before leaving the clinic after dosing and completion of the post-dosing on-site confinement, participants will be given a diary card and receive guidance on how to fill in the card. All participants will receive a digital thermometer to record temperature. Participants who receive an IM dose will also receive a ruler to measure diameter of redness and/or swelling at the injection site, if present.

The diary card will be used by the study participants to record the duration, and intensity (refer to Section 8.2.3.1) of solicited injection site AEs (for participants who receive an IM dose) and solicited systemic AEs up to Day 7 following injection or infusion for all participants. This information should be recorded in the participant diary card at approximately the same time each evening, through Day 7 (refer to Section 8.2 for more information).

The diary card will be collected and reviewed by the investigator (or designee) on the Day 8 Visit for both the Dose Escalation Phase and the Dose Expansion Phase participants.

No changes to the diary card will be permitted; however, any verbally recalled information provided by the participant during review of the diary card will be documented in the source document and reported as an AE as applicable.

Memory aid

A memory aid will be utilized by participants to collect unsolicited AEs beginning at discharge from the clinic, through Day 151 (end of study participation for an individual). Participants will be instructed to record unsolicited AEs whenever they occur, recording such AEs on the memory aid. The memory aids will be collected and reviewed by site staff at each subsequent visit through the end of the study.

8.1.10. Participant Follow-Up

Participants will be instructed to contact a study team member to report new or worsening AEs, as well as new diagnoses, and to come to the study clinic if medical attention is needed.

For emergencies and other unscheduled visits to a medical facility other than the study clinic, medical records will, to the extent possible, be obtained by the investigator.

Participants will be asked about the occurrence of AEs, SAEs, AESIs, receipt of concomitant prescription medications/vaccinations, and change in general health status and any other change in status that may affect the participant's participation, as indicated in the SoA.

Any deviation from protocol procedures, evaluations, and/or visits will be documented.

8.2. Adverse Events and Serious Adverse Events

Local injection site solicited AEs will include pain, redness and swelling, and will be assessed after dosing at Visit 1 for 7 days (IM recipients only). If more than 1 injection is given, reactions will be assessed separately at each injection site.

Systemic solicited AEs will be assessed in all participants after dosing at Visit 1 and recorded for 7 days. These will include fever, headache, fatigue, muscle aches, nausea, vomiting, diarrhea, and joint pain.

Site staff will document any AEs in the study source during the confinement for all cohorts. The site staff will record solicited injection site AEs (IM doses only) and solicited systemic AEs (all participants), including duration and intensity, during confinement. Refer to Section 8.1.9 for solicited AEs to be recorded in the diary card by participants, through Day 7.

Solicited AEs that continue beyond Day 7 will be captured in the unsolicited AEs memory aid and marked as continuation of solicited AE. Participants will be asked to record events at the same time each evening.

Unsolicited AEs including AESIs, SAEs, and safety laboratory parameters Grade 1 and above will be collected from screening through Day 151 and recorded in the AE log by the study team.

The definitions of AEs, SAEs, serious adverse drug reactions (ADRs) and AESIs can be found in Appendix 2, Section 10.2.1, and 10.2.2, 10.2.3, 10.2.4, respectively.

Refer to Appendix 2, Section 10.2 for details regarding AEs, AESIs, and SAEs and Section 10.4 (Table 9) for laboratory parameters.

Immediate safety concerns should be discussed with the sponsor, and the SRT. The SRT will trigger an IDMC review if any pausing rule is met (see Section 8.2.7 for IDMC and Section 10.2.5 for details regarding AE reporting and follow-up).

AEs will be reported by the participant (or, as appropriate, the participant's legally authorized representative). Clinical chemistry and/or hematology results may also qualify as AEs (Section 10.4, Appendix 4).

Study nurses and physicians are responsible for collecting and documenting information and events that would potentially meet the definition of an AE. However only the investigator or sub-investigator is responsible for assessment, including assignment of causality and, for unsolicited AEs, the intensity, and for reporting and management of all AEs. The investigator is responsible for following up all AEs regardless of their relatedness to study intervention or study procedures, or AEs that caused the participant to withdraw from the study (Section 7).

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

Type of Event	Collection Time Period
All solicited AEs	Day 1 through Day 7 (inclusive)
Unsolicited AEs, and SAEs including AESIs	Screening through end of study (Day 151)

Distribution and collection days for diary cards and memory aids are shown in the SoA.

Medical conditions that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not in the AE section.

All SAEs and AESIs will be reported to the sponsor or designee within 24 hours, as indicated in Appendix 2, Section 10.2.6. The investigator will submit any updated SAE and AESI data to the sponsor or designees within 24 hours of it being available.

Investigators are not obligated to actively seek AEs, SAEs or AESIs after a participant concludes study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be related to the study intervention or study participation, the investigator must notify the sponsor or designee within 24 hours.

8.2.2. Method of Detecting AEs and SAEs

The methods of recording and follow-up of AEs, SAEs and AESIs are provided in detail in Appendix 2, Section 10.2.5, which includes assessments of intensity, relationship to the study intervention, and outcome of AEs, SAE and AESIs.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading questions are the preferred method to inquire about AE occurrences.

8.2.3. Follow-up of AEs

After the initial SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs/AESIs will be followed until resolution, stabilization, or the participant is withdrawn/withdraws, or is lost to follow-up or (as defined in Section 7.2 and Section 7.3, respectively). Refer to Appendix 2, Section 10.2.5.4.

8.2.3.1. AE Intensity

The intensity of AEs will be classified by the investigator based on the toxicity grading tables (Section 10.4 Appendix 4). In the case of an AE or abnormal clinical laboratory result not included in Appendix 4, intensity will be assigned using the Grades described in the U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events, Version 5.0 [US HHS 2017] (See Section 10.2.5.1).

Local solicited AEs will be recorded on the diary card by the participant and graded and/or measured by the participant. An exception is that the study investigators will grade solicited AEs

during the confinement period. Any participant-reported Grade 3 or higher adverse event will be assessed by the investigator.

8.2.3.2. AE Causality/Relationship to Study Intervention

All AEs will be evaluated by the investigator or medically qualified designee (i.e., investigator, sub-investigator) to assess the relationship between study intervention and the AE (with the exception of local injection site reactions, which are assumed to be related to the injection). Careful medical judgment should be exercised to determine the level of causal relationship between an AE and the study intervention. The causality will be assessed as either related or not related.

The sponsor or designee will have the opportunity to confirm the seriousness and case causality based on the clinical judgment of the Medical Monitor or sponsor designee. If a serious adverse event is considered unrelated by the investigator but the sponsor believes that there is a reasonable possibility that the event is related, the sponsor will upgrade the case to a 'related' status. The sponsor or designee will never downgrade a case from serious to non-serious or change the investigator assessment of causality from related to not related.

Refer to Appendix 2, Section 10.2.5.2 for details.

8.2.4. Regulatory Reporting Requirements for SAEs

Refer to Appendix 2, Section 10.2.6 for details regarding SAE reporting.

The sponsor or delegate has a legal responsibility to notify both the local regulatory authority and potentially other regulatory agencies about the safety of the study intervention under clinical investigation. Therefore, prompt notification by the investigator to the sponsor of a SAE is required.

The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

In the U.S., the sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator all SAEs including SAEs associated with the use of the study intervention. The investigator must report these events to the appropriate IRB that approved the protocol, unless otherwise required and documented by the IRB.

AEs reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

The sponsor will prepare, distribute, and submit Serious ADR reports according to local regulatory requirements of participating countries.

Refer to Appendix 2, Section 10.2.6 for details regarding SAE reporting.

8.2.5. Death Events

Any untoward medical occurrence (AE) resulting in death is reported as an SAE. The cause of death will be appropriately documented in the SAE report form and supporting evidence will be provided.

8.2.6. Safety Review Team

A SRT will be established as the team responsible for recommending dose escalation or dose expansion to the sponsor's Chief Medical Officer. The SRT will operate according to the Safety Review Team Plan.

Meetings of the SRT to provide a recommendation on dose escalation or dose expansion will occur during the Dose Escalation Phase when all participants in the current***ly dosed*** cohort have completed Day 15. The SRT will also meet approximately every 8 weeks during the Dose Expansion Phase. The SRT will review all available blinded safety data collected at the time of the review to determine whether or not any pausing event has occurred (See Section 7.1.1.). If a pausing event does not occur, dose escalation or moving to the Dose Expansion Phase cohort will be recommended by the SRT.

If a pausing rule is met, the SRT will ask the IDMC to conduct a review of unblinded safety data. The IDMC will make a recommendation to the sponsor regarding the further conduct of the study.

8.2.7. Independent Data Monitoring Committee

The IDMC will operate according to a charter approved by the sponsor and all IDMC members. The IDMC structure, participants and other details will be provided in the charter. The charter will be approved prior to enrollment of the first study participant.

The role of the IDMC will be to (a) review unblinded safety data if a pausing rule is met and (b) make recommendations to the sponsor on further conduct of the study if a pausing rule is met.

The recommendations of the IDMC, along with the sponsor's decision, will be communicated to the investigator, to the responsible IRBs/IECs and to the US FDA.

8.3. Treatment of Overdose

Overdose of any study intervention (including Placebo) is unlikely to occur since the injections and infusions are administered as a single dose by a trained study staff member. If an overdose were to occur, the overdose, including misuse or abuse of the product and medication errors, should be reported in in the clinician notes and the eCRF. If an overdose error occurs, the participant will be monitored for symptoms and provided with necessary supportive care.

8.4. Blood Sampling

Refer to the SoA for blood sample collection at screening for eligibility and safety laboratory assessments. Blood samples will be collected for pregnancy test, HIV, hepatitis B, hepatitis C and safety laboratory assessments as described in Section 8.1.7.

Whole blood samples will be collected for measurement of PK, ADA, and RSV neutralizing antibodies. At Visit 1, all samples will be collected prior to dosing.

A total of approximately 200mL of whole blood will be collected from each participant during the entire study period assuming all planned samples are collected, according to the SoA.

8.5. Pharmacokinetics

Dose Escalation Phase: At Visit 1, PK blood draw will occur at pre-dosing, 1 hour (+/- 30 minutes) before administration of IM injection or beginning of infusion, for all participants in Cohorts 1-4. For participants who receive IV study intervention, the timing of post-dose blood samples begins at the end of the IV infusion. Samples are obtained at 5 minutes (± 1 minute) at 8-hours (± 0.5 hour) and at 24-hours (± 1 hour) after the end of the infusion. For participants who receive IM study intervention, the timing of post-dose blood samples begins at the time of the IM injection and samples are obtained at 8-hours (± 0.5 hour) and at 24-hours (± 1 hour) after the IM injection.

Dose Expansion Phase: At Visit 1, only a pre-dose sample, collected 1 hour (+/- 30 minutes) before administration of IM injection is obtained at Day 1.

Blood for PK samples at all visits after Day 1 will be obtained according to the SoA as shown in Table 2 and Table 3.

For all samples, the actual date and time (24-hour clock) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.

Whole blood samples in serum separator tubes and VAMS will be collected for measurement of RSM01 concentrations in serum and capillary blood, respectively, as specified in the SoA. The quantification of RSM01 in serum and capillary blood will be performed using a validated immunoassay method. Concentrations will be used to evaluate the PK of RSM01. The PK parameters specified in the endpoints will be calculated.

Remaining samples collected for analyses of RSM01 may also be used to evaluate immunogenicity and/or safety aspects related to any concerns arising during or after the study. Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of the study are specified in the ICF.

8.6. Pharmacodynamics

For this study, pharmacodynamics is being assessed as an exploratory endpoint. A surrogate pharmacodynamic marker will be used, measuring the ex vivo capability of RSM01 to neutralize RSV.

Whole blood samples in serum separator tubes and VAMS devices will be collected for detection of RSV neutralizing antibodies in serum and capillary blood respectively, as specified in the SoA. Samples on Day 1 will be collected prior to RSM01 administration.

The quantification of RSV neutralizing antibodies in serum and capillary blood will be performed using a validated viral neutralization method. This method will detect both RSM01 and neutralizing anti-RSV antibodies from prior natural infection. Therefore, the Day 1 sample is needed to evaluate changes in neutralization responses, post-treatment.

Remaining samples collected for analyses of RSV neutralization may also be used to evaluate drug concentration, immunogenicity, and safety aspects related to concerns arising during or after the study. Details on processes for collection and shipment of these samples are in the

Laboratory Manual. Retention time and possible analyses of samples after the end of the study are specified in the ICF.

8.7. Genetics

No genetic testing will be performed for this trial.

8.8. Biomarkers

There are no prospective biomarker analyses planned.

As dictated by clinical data and emerging science, the non-genetic biomarkers may be added during trial execution. These will be clearly documented in the clinical study report (CSR) and/or the trial master file (TMF).

Clinical safety laboratory assessments such as hematology may also be included as exploratory biomarkers in pre-specified analysis plans.

8.9. Immunogenicity

Whole blood samples in serum separator tubes and VAMS samples will be collected for detection of ADA against RSM01 in serum and capillary blood respectively, as specified in the SoA. 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 ADAs may be further characterized.

Remaining samples collected for analysis of anti-RSM01 antibodies may also be used to evaluate RSM01 concentration or exploratory biomarkers during or after the study. Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of the study are specified in the ICF.

9. Statistical Considerations

9.1. Sample Size Determination

This trial is an exploratory trial to characterize safety, tolerability, and pharmacokinetics of single doses of RSM01 mAb. The trial is designed to be descriptive and is not based on formal testing of a null hypothesis. Therefore, this study is not powered to detect any differences in potential safety data between treatment groups. Approximately 56 participants will be available for analysis: 28 participants in the Dose Escalation Phase and 28 participants in the Dose Expansion Phase.

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

Safety

With 6 participants (per RSM01 arm in each 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 24 participants (across all 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 doses of RSM01 (48 participants), there is approximately 80% (90%) power to observe at least one AE if the true AE rate is 3.3% (4.68%).

9.2. Populations for Analyses

Analysis populations are shown in Table 6.

Table 6: Populations for Analyses

Population	Description
Intention to treat (ITT) PK population	All participants who received the study intervention. Participants will be analyzed according to the intervention actually received.
Per protocol (PP) PK population	All participants who received RSM01 and did not significantly deviate from study procedures, and who have at least one, non-zero PK result available. Participants will be analyzed according to the intervention actually received.
Safety	All participants who received the study intervention. Participants will be analyzed according to the intervention actually received.
Immunogenicity population	All participants who received the study intervention and have at least one valid ADA result. Participants will be analyzed according to the intervention actually received.

9.3. Statistical Analyses

A detailed statistical analysis plan (SAP) centered on primary and secondary endpoints will be developed and finalized prior to unblinding the study and will further describe the participant populations to be included in each analysis, details of the statistical methods, including procedures for accounting for missing, unused, and spurious data. Some exploratory analyses, not associated with exploratory endpoint analyses, may be included in this SAP. Analyses are summarized in Table 7.

Exploratory endpoint analyses, in particular, those centered on exploratory biomarker analyses, and details for PD and serum PK/ADA analyses, will be described in a separate exploratory scientific and statistical analysis plan (exploratory SSAP). Specific objectives and hypotheses related to exploratory biomarker analyses will be documented in this exploratory SSAP prior to full data unblinding and analysis.

Results from the exploratory analyses may be reported in a separate results memo and included as an addendum to the CSR.

Table 7: Summary of Primary and Secondary Endpoints and Analyses

Endpoint	Statistical Analysis
Primary:	
Unsolicited AEs through Day 151 All SAEs/AESIs through Day 151 Solicited systemic AEs through Day 7 Solicited local AEs for injection site reactions for 7 days after dose administration (only applies to IM doses)	The incidence and Clopper-Pearson 95% CIs of AEs and SAEs/AESIs will be summarized by treatment group, dose levels, routes of administration and overall, and by intensity. Duration, day of onset of local and systemic solicited AEs will be summarized by group. Relationship of unsolicited AEs and SAEs/AESIs to the study intervention will be summarized by group. Any infusion reactions will be described.
Secondary:	
Safety laboratory parameters Grade 1 and above through Day 151	The incidence of safety parameters outside of normal ranges (Grade 1 and above), change from baseline, grades, grade shifts, as applicable, will be summarized by treatment group, dose levels, routes of administration and overall, and by intensity, and relationship to the study intervention.
PK parameters AUC0-∞, CD_{91}, $AUC_{0\text{-}D91}$, CD_{151}, $AUC_{0\text{-}D151}$ Cmax, Cmin, Tmax, t1/2, CL and Vz	RSM01 capillary blood concentrations and PK parameters will be summarized by treatment group using descriptive statistics, and the number of participants. Following summaries will be provided arithmetic mean, standard deviation, arithmetic percent CV, median, minimum, maximum, geometric mean, and geometric percent CV. The proportion of participants with observed or predicted CD_{151} concentrations above the EC90 will be summarized by treatment group and country, as appropriate.
Incidence of ADAs to RSM01 through Day 151	ADA incidence will be summarized by treatment group. Exact analyses will be pre-specified in the SAP.

9.3.1. Safety Primary Endpoints

The primary analysis will occur when all participants reach Day 151. All safety summaries will be presented for all participants in the safety population.

Solicited Local and Systemic AEs

All solicited local AEs will be considered study intervention-related events and will be summarized for each injection site.

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 intensity, 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 AE with maximum severity will be used for tabulations.

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

Unsolicited Treatment Emergent AEs, SAEs and AESI

All unsolicited AEs, serious adverse events (SAEs), and/or AESI will be recorded from screening through Day 151.

Unsolicited AEs, SAEs, AESI will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC), Preferred Term (PT) and greatest intensity. Clopper-Pearson exact 95% CIs will be calculated on the percentages. 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, one or more SAE, and/or 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 intensity 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 AE with maximum intensity will be used for tabulations. Participants reporting more than one occurrence for the PT term level being summarized will be counted only once.

9.3.2. Safety Secondary Laboratory Assessments

Clinical safety laboratory evaluations are listed in Section 8.1.7. All laboratory values collected at visits will be included in the summaries and listings. Descriptive summaries (n, mean, standard deviation, median, minimum, and maximum) of observed value and change from baseline (last result available on or before Day 1) at each scheduled post baseline visit will be presented for each continuous variable test parameter.

Summaries by toxicity grade and grading shifts in laboratory values from Day1 (baseline) to Day 8, Day 91, and Day 151 visits will be also presented.

The frequency of safety laboratory parameters outside the normal range will be summarized by treatment group.

9.3.3. Other Safety Measures

Vital signs, 12-Lead ECG, medical history, and summary statistics will be tabulated by treatment group. Any other relevant information will be presented in participant data listings. Further details will be provided in the SAP.

9.3.4. Pharmacokinetics

All available PK data will be summarized at the time of dose selection for the Dose Expansion Phase, and for the interim and primary analyses when all participants reach Day 91 and Day 151, respectively.

RSM01 capillary blood concentrations and the following PK parameters, $AUC_{0-\infty}$, , $AUC_{0-t,}$ C_{min}, C_{max} ,or C0, C_{D91}, C_{D151}, T_{max}, $t_{1/2}$, CL and Vz, will be summarized by treatment group. Each of the PK parameters will be summarized using descriptive statistics (e.g., arithmetic mean, standard deviation, arithmetic percent CV, median, minimum, maximum, geometric mean, and geometric percent CV), and the number of participants, as appropriate.

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.

PK will be summarized in the PP PK population.

In addition to calculating the PK parameters using noncompartmental analysis (NCA) methods, RSM01 capillary blood and venous serum-concentration data obtained in this study will be used to develop a population PK model that will aid in the prediction of dose or doses to be administered in infants and to assess potential covariates. The venous serum will be used for developing the model and not for the NCA analysis.

This analysis will be described in an independent analysis plan and reported separately.

9.4. Serum and Capillary Blood Immunogenicity

All available ADA results will be summarized for each treatment cohort at the time of the primary analyses, when all participants reach Day 151.

Further details will be specified in the SAP for capillary blood analyses and in the exploratory SSAP for serum.

9.5. Serum and Capillary Blood RSV Neutralizing Antibody

All available serum RSV neutralizing antibodies will be summarized for each treatment cohort at the time of the primary analysis, when all participants reach Day 151

Analyses will be specified in the exploratory SSAP.

9.6. Demographic and Compliance Analyses

Demographic parameters (age, sex, and race/ethnicity) and other baseline characteristics will be summarized descriptively by treatment group for all participants in the safety population.

Listings of randomized participants with protocol deviations (to be defined in the SAP) will be presented by treatment group.

9.7. Interim Analyses

An interim analysis is planned for this study when all participants in each of the Dose Escalation Phase cohorts have completed Day 91. 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/s to be administered to infants and to assess covariates.

The purpose of this interim analysis will be to inform on the broader program; 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 to whom the results will be provided to will be outlined in a separate document (which will be finalized prior to the interim analysis).

The interim analysis will be performed by an unblinded statistician. The investigator will be blinded. The sponsor and/or sponsor's designee(s) will review aggregated safety data by cohort only (including data from both RSM01 and Placebo participants) and will review aggregated PK data by treatment group (RSM01 vs. Placebo) within and across cohorts. Although the sponsor will be blinded throughout the study, such review of aggregated data could potentially lead to unblinding of the treatment received by individual participants.

9.8. National Regulatory Authority

The national regulatory authority will receive all expedited safety reports from the clinical trial and have the authority to terminate, suspend or require changes to a clinical trial.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

a. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

b. Applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines

c. Applicable laws and regulations

d. The protocol, protocol amendments, ICF, and other relevant documents (e.g., diary cards) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated

e. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

10.1.2. Study Oversight

The study sponsor, the institution through which the research is performed and all members of the investigator's clinical team and the national regulatory authority share responsibility for ensuring the safety of participants in this trial.

The investigator will be responsible for the following:

a. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/IEC

b. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

c. Providing oversight of the conduct of the study at the site and adherence to requirements of ICH and GCP guidelines, national authority regulations, the IRB/IEC, and all other applicable country and local regulations

d. Closely monitoring study participants and taking whatever measures necessary to ensure their safety. The investigator may delay an individual's study intervention administration or pause study intervention administration altogether if the investigator is concerned that the study intervention might place a participant or participants at significant risk. Where specified, the responsibilities of the investigator may be delegated to a medically qualified team member (designee). The investigator determines intensity and causality with respect to the study intervention for each AE.

The sponsor has an institutional responsibility to ensure participant safety and is ultimately accountable for safety oversight. Medical monitors and the IDMC play an important role in this regard and support the sponsor.

The Medical Monitor is the sponsor's representative and is a physician. The Medical Monitor:

a. reviews the safety of the product for protocols in a specific region and, in consultation with the sponsor
b. is responsible for safety oversight in-country and plays an important role in the reporting of Serious ADRs, SAEs, pregnancies, and other important safety information, as described in the protocol
c. in consultation with the sponsor, may assess the intensity and causality for AEs and may upgrade the degree of intensity and causality that has been determined by the investigator or designee

The Medical Monitor, like the investigator, will be blinded until primary endpoint analyses are completed, unless emergency unblinding is required.

The Institutional Review Board or Ethics Committee has institutional responsibility for the safety of research participants. The Institutional Review Board or Ethics Committee has the authority to terminate, suspend or require changes to a clinical trial.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

The investigator or designee will explain the study to the participant and answer all questions regarding the study. The investigator or designee will conduct the consent discussions on an individual basis with each participant. Adequate time will be allowed for all questions to be addressed. Potential participants will be interviewed to ensure that they meet all entry criteria relating to history.

Written informed consent will be obtained prior to conducting any study-related procedures.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of FDA Code of Regulations (CFR) 21 CFR 50, local regulations, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and the IRB/IEC or study center.

Written informed consent must obtained before the participant is enrolled in the study, and the date the written consent was obtained must be documented. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF must be provided to the participant.

10.1.4.1. Informed Consent Forms

Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period. Any test results from the samples collected before withdrawing consent may still be used for the study.

The informed consent form will be obtained by the use of a written ICF approved by the IRB/IEC and signed and dated by the participant.

A copy of the signed consent form/s shall be given to the participant prior to conducting any study-related procedures.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If there is a change to the ICF during the conduct of the study, participants must be re-consented using the most current version of the ICF.

Any withdrawal of consent for sample testing will be documented in the CRF.

If a participant cannot be randomized on the intended day of dosing (e.g., due to elevated temperature) he/she is not required to sign another ICF, as long as re-screening and dosing occur within the protocol-defined window.

10.1.5. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant record or dataset that is transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the sponsor.

The participant must be informed that the participant's study-related data will be used by the sponsor in accordance with local data protection law. The level of data disclosure must also be explained to the participant.

The participant must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Dissemination of Clinical Study Data

Study information from this protocol will be posted on publicly available clinical trials registers (for example, clinicaltrials.gov) before enrollment of participants begins. Summaries of the results of the study will also be posted on the same website.

The final CSR will include all available data through the final study visit. The database will be locked prior to preparation of the final CSR when all of the above data have been entered, reviewed, and all queries related to the data have been addressed.

Modifications or additions to the analyses will be included in the relevant analysis plan. Any decisions to deviate from the planned analyses described in the protocol and in the SAP will be described in detail in the final CSR. The CSR will be reviewed and approved by the sponsor signatory and the lead investigator.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded by an electronic CRF using an EDC system or transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

The investigator must maintain accurate documentation that supports the information entered in the eCRF.

The study will be monitored regularly by the sponsor or its designee throughout the study period. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible checking the accuracy and completeness of the data reported in the eCRFs and the consistency with the source documents. The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations [CROs]).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Source Documents

Source documentation consists of existing medical records and/or study records developed and maintained by the investigator. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

Data recorded on source documents will be transcribed onto electronic case report forms (eCRFs) using an EDC system.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.

For the purpose of monitoring and auditing the study, source documentation will consist of existing medical records and/or study records developed and maintained by the investigator.

10.1.9. Record Retention

Records and documents pertaining to the conduct of this study must be retained by the investigator for a minimum of 10 years after study completion unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.10. Study and Site Closure

The sponsor reserves the right to close the study site(s) or terminate the study at any time for any reason at their sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

d. Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
e. Inadequate recruitment of participants by the investigator
f. Discontinuation of further study intervention development.

At the discretion of the sponsor, all materials and supplies provided to the investigator will be returned or disposed of in compliance with local regulatory requirements upon authorization from the sponsor, upon study completion. The investigator or designated clinical site staff will notify the IRB/IEC when the study has been completed.

10.1.11. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
An AE is 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. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2.3. Definition of Serious Adverse Drug Reaction (Serious ADR)

When an AE is judged to be serious and related to an investigational product, it is a Serious Adverse Drug Reaction and is subject to expedited reporting based on the parameters of this study.

10.2.4. Definition of AESI

AESIs are AEs that the sponsor will carefully monitor. The following AEs will be collected and reported as AESIs: anaphylaxis or hypersensitivity reactions, and/or infusion reactions resulting in permanent discontinuation of study intervention infusion during IV administration.

10.2.5. Recording and Follow-Up of AE, SAE, AESI

Recording

Care will be taken not to introduce bias when detecting AEs, SAEs and AESIs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all available documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will record all relevant AE/SAE/AESI information in the CRF.

AEs will be reported on the AE CRF using a recognized medical term or diagnosis that accurately reflects the event.

AE evaluations will be reviewed by the investigator or a medically qualified delegate. AE CRF pages are to be completed by members of the study team who are designated to perform this task by the investigator. The onset and resolution dates of an AE and action taken in response to the AE will be documented.

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE/AESI CRF page.

There may be instances when copies of medical records for certain cases are requested by the Medical Monitor, the SRT, the IDMC and/or the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.

AEs/SAEs/AESIs will be assessed for intensity and causal relationship to the study intervention. Note that local AEs reported within the first 7 days after IM dosing are considered to be study intervention-related.

Follow-up and Resolution

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE/SAE/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology, if available.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of receipt of the information.

The onset and resolution dates of the event and medical care provided in response to the event will be documented.

AEs will be considered resolved when the condition returns to normal or returns to the participant's baseline status as established on Study Day 1, or when the condition has stabilized with the expectation that it will remain chronic.

If the event has not resolved by the final study visit, it will be documented as "ongoing" on the CRF, however, follow-up of the SAE/AESI must continue until resolved or the condition has stabilized. Information recorded on the CRF must be substantiated in the source documents.

The resolution date to be recorded on the CRF is the last date on which the participant experienced the AE.

10.2.5.1. Assessment of Intensity

The investigator will assess the intensity of each AE reported during the study. In the case of local reactions, vital signs, systemic events, and laboratory abnormalities, the Grades delineated in Section 10.4, Appendix 4 will be employed.

In the case of an AE or abnormal clinical laboratory result not included in Appendix 4, intensity will be assigned using the Grades described in the U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events, Version 5.0 [US HHS 2017] as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**symptoms, causing inability to perform usual social and functional activities with intervention or hospitalization indicated

Grade 4 Life-threatening consequences; urgent intervention indicated

Notes:

A semi-colon indicates 'or' within the description of the grade.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.5.2. Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/AESI. Only AEs that are local reactions to an IM injection are automatically assumed to be related to the study intervention, and therefore are not required to have causality assessed by the investigator.

The investigator will assess whether the AE/SAE/AESI is either:

Related: An AE/SAE/AESI is considered related to study intervention if there is a reasonable possibility that the study intervention contributed to the AE.

or

Not related: There is no reasonable possibility that the AE/SAE/AESI is causally related to administration of the study intervention. There are other more likely causes for the AE.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

For each AE/SAE/AESI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AESI and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to assess causality to include in the initial report. However, **it is very important that the investigator always provide makes an assessment of causality with the initial submission of the SAE data.**

The investigator may change his/her assessment of causality when considering additional follow-up information and submit an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements applicable to SAEs.

10.2.5.3. Assessment of Expectedness

Not applicable

10.2.5.4. Assessment of Outcome

The outcome of each SAE/AESI must be reported. For analysis purposes, the outcome for serious adverse events will be determined on the final study visit.

Outcome of all AEs will be classified as one of the following:

•Resolved

•Resolved with sequelae

•Ongoing

•Death.

10.2.6. SAEs, AESIs, and Serious ADR Reporting

Reporting to Sponsor or Delegate Via the Electronic Data Collection Tool

The primary mechanism for reporting an SAE or AESI by the investigator to the sponsor or delegate will be the electronic data collection tool.

The site will enter the SAE or AESI data into the electronic system as soon as it is identified.

All SAEs (related and unrelated) and AESIs are reported to the sponsor or delegate throughout the study.

Serious ADRs are reported to the sponsor or delegate during the entire study period. Serious ADRs are to be reported after completion of the study, if the investigator becomes aware of a serious ADR.

The investigator must not wait to collect additional information to fully document the event before notifying the sponsor or delegate of a SAE or an AESI. The initial notification should include the following:

- Protocol number and name and contact number of the investigator
- Participant ID number (and initials and date of birth, if available)
- Date participant received study intervention
- SAE/AESI term and date of event onset
- Current status of SAE/AESI

The investigator is responsible for expedited safety report submission to the sponsor delegate and the sponsor delegate reports to the national regulatory authority(ies) within specific time periods of being notified of the event. Therefore, it is important that the investigator submit additional information requested as soon as it becomes available.

Original and follow-up reports must be submitted according to the requirements of the regulatory authorities.

If the electronic system is unavailable, the site may use the paper SAE/AESI data collection tool (see next section) instead of the EDC, in order to report the event within 24 hours of becoming aware.

After the study is completed at a given site, the electronic data collection tool, if used, will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

Contacts for SAE/AESI reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the study sponsor.
Reporting via Paper CRF
If the eCRF cannot be completed, the Supplemental SAE/AESI Report (paper form) should be completed by the investigator or his/her designee, and scanned and emailed, or faxed to the sponsor or delegate. The investigator is responsible for ensuring an adequate transmission of the fax and will store the distribution confirmation in the study file. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE/AESI report form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE/AESI CRF pages within the designated reporting time frames.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Contraceptive Guidance:

Male participants with partners of childbearing potential must agree to use condoms during the study and for 90 days after the study, and they must refrain from sperm donation for at least 90 days after the end of study.

Female participants of childbearing potential must not be pregnant, breastfeeding, or attempting to become pregnant for 28 days before Screening and throughout the duration of the study. These participants must have a negative serum pregnancy test at Screening in order to be eligible for randomization and treatment with study intervention. In addition, these female participants must be willing to commit to using a consistent and acceptable method of contraception for the duration of the study and for 90 days after study completion if they engage in intercourse. Acceptable methods of contraception are:

- Consistent use of systemic contraception, including birth control pills, transdermal patch, vaginal ring, implants, and injectables.
- Consistent use of double barrier method, e.g., condoms, cervical cap, diaphragm, vaginal contraceptive film with spermicide.
- Use of intrauterine device with a low failure rate (defined as < 1% risk of pregnancy per year)
- Monogamous intercourse with a vasectomized man or has only same-sex partners.

Female participants who are not sexually active but become so during the study must agree to follow the contraceptive requirements above.

Female participants who are not of childbearing potential must meet at least one of the following criteria:

- At least 1 year since the last menstrual period.

- Surgically sterile (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy)
- Congenitally sterile
- Diagnosed as infertile and not undergoing treatment to reverse infertility.

Collection of Pregnancy Information:

- A participant who becomes pregnant during the study period will be asked to complete all visits and procedures through Day 151 as described in Table 2 or Table 3, as applicable. After she completes Day 151, or in the event that she voluntarily withdraws from the study and agrees to provide additional information regarding the pregnancy, the investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate. Neonate follow-up will occur for 6 weeks beyond the estimated delivery date.
- If a participant is determined to be pregnant during the study (after receiving a dose of the study intervention), the investigator will report the pregnancy to the sponsor or delegate and collect follow-up information on the participant and the neonate. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy is not considered to be an AE or a SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or a SAE. Any abnormal pregnancy outcome that comes to the attention of the investigator (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) is considered to be a SAE.
- Any pregnancy-related SAE that occurs after study participation and is made known to the investigator and is assessed as related to the study intervention will be reported to the sponsor or the sponsor's designee. The investigator is not obligated to actively seek such information in former study participants who become pregnant during the study.

10.4. Appendix 4: Toxicity Tables

The following toxicity tables are extracted from the FDA Guidance for Industry [FDA 2007].

Table 8: FDA Toxicity Grading Scale- Clinical Abnormalities

Local Reactions

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Table 8: FDA Toxicity Grading Scale- Clinical Abnormalities-

Vital Signs

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock

Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy populations, for example, conditioned athletes.

Table 8: FDA Toxicity Grading Scale- Clinical Abnormalities, continued…

Systemic Events

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Table 9: FDA Toxicity Grading Scale- Laboratory Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperos-molar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

***ULN is the upper limit of the normal range.

Table 9: FDA Toxicity Grading Scale- Laboratory Abnormalities, continued…

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

WBC= white blood cell count

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

GGT grading is not provided in the FDA toxicity grading scale tables. The following grading scale is from the U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events, Version 5.0 [US HHS 2017]:

- Grade 1: >ULN - 2.5 x ULN if baseline is normal; 2.0 - 2.5 x baseline if baseline is abnormal
- Grade 2: >2.5 - 5.0 x ULN if baseline is normal; >2.5 - 5.0 x baseline if baseline is abnormal
- Grade 3: >5.0 - 20.0 x ULN if baseline is normal; >5.0 - 20.0 x baseline if baseline is abnormal
- Grade 4: >20.0 x ULN if baseline is normal; >20.0 x baseline if baseline is abnormal.

Table 10: FDA Toxicity Grading Scale- Urine

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

11. References

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12. Protocol Version History

The Protocol Version updates and amendment summary of changes is provided below.

- **Version 1, dated 26 May 2021**
- **Version 1.1, dated 09 June 2021**
- **Version 2.0, dated 20 July 2021**
- **Version 3.0, dated 10 December 2021**
- **Version 4.0, dated 21 January 2022**

Version 1.1, dated 09 June 2021

Rationale for changes to V1: The update from Version 1 to Version 1.1 was made prior to study start and prior to IRB approval, and was issued as a response to a preliminary review by the IRB, and internal reviews of supporting documents. For this reason, the update was not considered as a protocol amendment.

- Section 5.1 Inclusion Criteria; recommendation: Since the apparent terminal half-life of the drug in monkeys is around 20 days, the Board recommends ensuring male contraception is used for duration of the study (5 months) to surpass the 5x t1/2 time window.

text added: ***For male participants who have a female partner of childbearing potential or a pregnant partner: condom use for the duration of the study period (approximately 5 months).***

- Section 5.4 Screen Failures; edited as follows:

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently ~~randomized to~~ ***entered into the study and do not receive*** study intervention~~/entered in the study.~~ A minimal set of screen failure information is required to ensure transparent reporting of ~~screen failure~~ ***criteria for*** participants ***who are screen failures in order*** to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria ***not met***, and any SAE.

Screening assessments can be done at any time during the screening ~~interval,~~***window (Day -30 to Day -2; SoA, Section 1.3),*** except for ~~the~~ written informed consent, which must be completed prior to any screening procedure.

Re-screening is only permitted under ***one or more of*** the following conditions:

- If a participant presents with an acute illness ***on the*** day of ~~first~~ ***planned*** study intervention, e.g., elevated temperature, acute respiratory or gastrointestinal illness, or urinary tract infection (UTI), and meets all other ~~inclusion/exclusion~~ ***eligibility*** criteria and can be rescreened within the originally defined screening window (SoA, Section 1.3).
- ~~When~~If there are technical difficulties with phlebotomy at screening (e.g., laboratory reports hemolyzed blood), technical error in running the laboratory tests or an abnormal urine analysis due to menstruation or UTI, ***and the participant can be rescreened within the originally defined screening window (SoA, Section 1.3).***
- If a participant is ***undergoing*** screening ~~period~~ and the study reaches a pausing rule. The participant may ~~rescreen~~re-screen when and if the IDMC ~~provides approval to restart~~ ***recommends, and the Sponsor determines, that the*** study ***may continue***.

Repeat ***screening*** procedures may be performed as long as they are completed within the screening window. ~~Rescreened participants should be assigned the same participant number as for the initial screening.~~

- Section 7.2 Participant discontinuation or withdrawal.

Text added to be in line with changes made to ICF. ***If the participant leaves the study, the participant's medical information will still be used or shared to the extent allowed by law. Any leftover samples will be destroyed after testing is completed unless the participant withdraws consent to sample use, in which case the samples will be destroyed at that time. Any test results from the samples collected before withdrawal can still be included in the analyses.***

Text regarding diary cards and memory aids was clarified as requested by the IRB. Edits are shown below (new text= bold italics and old text= strike-through)

- Section 8.1.9 Diary card and Memory aid, edited as follows:

Diary Card
Before leaving the clinic after dosing ~~(Dose Escalation Phase, on Day 3~~ and ~~Expansion Phase on Day 1 or Day 2 depending on whether~~***completion of*** the ~~participant is kept overnight),~~***post-dosing on-site confinement***, participants will be given a diary card and receive guidance on how to fill in the card. ***All participants will receive a digital thermometer to record temperature***. Participants ***who receive an IM dose*** will also receive a ~~digital thermometer, mirror, and a~~ ruler ***to measure diameter of redness and/or swelling at the injection site, if present.***

The diary card will be used by the study participants to record the duration, and intensity (refer to Section 8.2.3.1) of solicited ~~local~~ ***injection site*** AEs ***(for participants who receive an*** IM ~~doses only)~~ ***dose)***, and solicited systemic AEs up to Day 7 following injection~~/~~ ***or*** infusion. ~~Unsolicited AEs will also~~ ***for all participants. This information should*** be recorded ~~if any occur during up to~~ ***in the participant diary card at approximately the same time each evening, through*** Day 7~~,~~ ~~including any local reactions reported after Day 7. The site staff will record duration and intensity of solicited local AEs (IM doses only) and solicited AEs while the participant is under confinement. This documentation of this information should be collected at approximately the same time each evening up to Day 7.~~

Memory aid

A memory aid will be distributed to the participant on ***the*** Day 8 ***visit*** and at each subsequent visit through Day 121 for Dose Escalation Phase cohorts and through Day 91 for the Expansion Phase cohort. Participants will be instructed to record unsolicited AEs ***whenever they occur,*** using the aid. The memory aids will be collected and reviewed with site staff at each subsequent visit through the end of the study.

- Section 8.2 Adverse Events and Serious Adverse Events

Site staff will document ~~the local~~ ***in the study source during the confinement for all cohorts. The site staff will record solicited*** injection site ***AEs (IM doses only)*** and ***solicited*** systemic ~~solicited AEs in the study source on Day 1~~***AEs (all participants), including duration*** and ~~2 for Cohort 2 and the systemic solicited AEs in the study source on Day 1 and 2~~***intensity, during confinement. Refer to Section 8.1.9*** for ~~Cohorts 1, 3, and 4. Site staff will document the local injection site and systemic~~ solicited AEs ~~in the study source on Day 1 for Cohort 5 if the participant is confined from Day 1 to Day 2. Participants will record their information on a~~ ***to be recorded in the*** diary card ~~(starting on Day 3 for the Dose Escalation Phase and on Day 1 in the~~

~~Expansion Phase or Day 2 if the participant is confined overnight) and will return the diary card to the site on Day 8.~~ ***by participants, through Day 7.***

Unsolicited AEs including AESIs, SAEs, and safety laboratory parameters Grade 1 and above will be collected from screening through Day 151 ***and recorded in the AE log by the study team.***

- Section 8.2.6 Safety Review Team

Edits made during review of the SRT plan. Members changed to 4 and added AESIs in text to be consistent with other text.

An ad hoc SRT meeting will occur immediately if any Grade 3 or higher AE, or SAE, ***or AESI,*** is reported, regardless of relationship to the study intervention. If the event is determined to be study intervention-related, the IDMC review will be triggered, and pausing will occur with enrollment and further dosing, until after the IDMC review.

The SRT will consist of a panel of at least ~~3~~***4*** members, including the Gates MRI ~~study physician~~ ***clinical lead***, ~~a~~ ***the*** Gates MRI ~~pharmacovigilance physician~~ ***safety lead***, ***the study Medical Monitor***, and the site principal investigator. The SRT members are part of the study team and will review blinded safety data.

- Section 8.8 Biomarkers

Text removed: ~~Samples collected during this clinical study may be transferred to a biobank and used for exploratory research outside the clinical protocol as described in the ICF. Transfer to the biobank will be documented and any testing of coded biobank samples will not be reported in the CSR.~~

- Section 10.1.4 and 10.1.14.1

Informed Consent and Process, deleted text that no longer applies to the study

Removed text that is no longer applicable: ~~The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature. Refer to (*section deleted*) for sample retention.~~

~~The ICF will contain a separate section that addresses the use of remaining mandatory samples for research not described in the protocol, e.g., assay development and assay quality control. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for research not described in the protocol.~~

~~Samples collected for storage for exploratory endpoint testing are included in the protocol and are not optional. However, consent for storage and testing of samples for research **not described in the protocol** is optional, and if not signed, would not exclude the participant from the study.~~

Version 2.0, dated 20 July 2021

Rationale for changes to V1: The update from Version 1.1 (v1.1) to Version 2 (v2), was prepared following FDA review and comments after IND submission. The major changes include the following:

In response to FDA's comment that *all adverse events should be collected throughout the dosing and follow-up period irrespective of who is collecting and documenting the event (i.e., participant vs. study site staff)*, the protocol was amended and text was aligned throughout. All adverse events (both solicited and unsolicited) will be collected throughout the dosing and follow-up periods (up to Day 151 for all participants) irrespective of who is collecting/documenting the event.

In response to the FDA's comment to use the same standardized toxicity grading scale consistently throughout entire protocol. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials, September 2007 was referenced consistently throughout the protocol and added textual reference to CTCAE version 5.0 for events not covered by the vaccine grading scales.

The pausing rules and contraceptive requirements were modified as recommended by the FDA.

Exclusion criteria were added for COVID-19 vaccine and for participants who previously received the study intervention in this study, based on Data Management and study team review regarding safety of the participant.

Other changes were considered minor to improve readability and clarity.

Complete List of Changes:

Title page and footer and header: change v1.1 to v2.0.

Added a page for Document History (Page 2)

Document History

Document	**Date**
Version 2.0	20 July 2021
Original Protocol v1.1	09 June 2021

Signature page: added v2

List of Abbreviations: Added ***for RSMO1*** to abbreviation for AUC, and of RSM01 to abbreviations for CD91, CD151, Cmax, Cmin and Tmax, deleted AKA for AUC, added NCT National (U.S.) Clinical Trial

Synopsis:

Dose Escalation Phase:

After the sentinel participant in each ***Dose Escalation Phase*** cohort receives RSM01, the next participant can be dosed 24 hours later, if there is no safety concern. ***After the 24-hour post-dose period for the sentinel participant in each cohort*** ~~On any given day, individual~~ participants in the Dose Escalation Phase cohorts should be dosed at least 2 hours apart regardless of ***route*** ~~mode~~ of administration (IM or IV). The ≥2-hour interval between administering IV infusions is to begin at the end of the previous infusion. For participants receiving the IM dose of study drug in Cohort 2, the ≥2-hour interval between administering IM injections to successive participants is to begin at the time of the previous participant's IM injection. If RSM01 is administered using 2 injections, the ≥2-hour interval begins at the time of the second injection.

Each dose escalation step will proceed after ***all participants in*** the prior cohort ***have***~~s~~ completed Day 15, and the Safety Review Team (SRT) has reviewed the data and determined that ***a pausing rule has not been met.*** ~~there are no events necessitating a pause.~~

Dose Expansion Phase:

Enrollment in the Dose Expansion Phase cohort (Cohort 5) will begin after Day 15 for ***all*** participants in Cohort 4, and after the SRT has reviewed the data and determined ***that a pausing rule has not been met.*** ~~no pausing event has occurred~~ Cohort 5 will include 28 participants randomized 6:1.

The~~ose~~ ***predictions suggest***~~s~~ that the concentration of RSM01 will be above the efficacy threshold (EC90) on Day 151 following a RSM01dose of 300 or 600 mg IM.

Synopsis

Pausing Rules: ~~Pausing rules include:~~

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 toxicity 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 and the U.S. Food and Drug administration (FDA) will be notified in an expedited manner.

- ~~at least 1 participant with a Grade 3 or higher AE (other than solicited AEs), considered related to the study intervention,~~
- ~~at least 1 participant with a SAE that is considered related to the study intervention~~
- ~~at least 1 participant with an AESI (AESIs include anaphylaxis, hypersensitivity reaction, and infusion reactions resulting in permanent discontinuation of the study intervention infusion during IV administration).~~

~~If a pausing rule is met, this will trigger a pause in enrollment and any dosing of participants, and an IDMC review of safety data will be conducted~~

IDMC: added: ***See Section 8.2.7.***

Safety Review Team: Meetings to decide on proceeding to each subsequent ***Dose Escalation Phase*** cohort will occur when ***all participants in*** the current cohort complete~~s~~ Day 15. ***The SRT will also meet approximately every 8 weeks during the Dose Expansion Phase (See Section 8.2.6).*** ~~The SRT will also receive an alert for any Grade 3 or higher AE or SAE and will determine if the AE/SAE is related to study intervention in order to trigger an IDMC review.~~

Visits: The participants in the Dose Expansion Phase cohort will remain at the clinic for at least 4 hours after dosing on Day 1, and possibly for the night of Day 1***, based on investigator decision.***

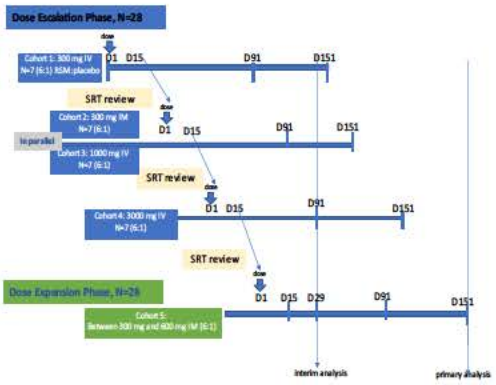
Blood Sampling: Dose Escalation Phase cohorts: On Day 1, PK blood draw will occur pre-dosing ***1 hour (+/- 30 minutes before administration of IM injection or beginning of infusion), at*** ~~within~~ 5 minutes (± 1 minute) after end of infusion for IV dosing only, and at 8-hours (±0.5 hour) and 24-hours (±1 hour) ***after end of infusion for IV doses and at 8-hours (±0.5 hour) and 24-hours (±1 hour) after IM dose*** ~~and at 8-hours post-dose for both the IV and IM dosing~~ ADA and RSV neutralizing antibody activity ***samples*** will be ***obtained*** pre-dose only ***(+/- 30 minutes) before administration of IM injection or beginning of infusion***

Dose Expansion Phase cohort: On Day 1, the blood collection for PK, ADA and RSV neutralizing antibody activity will occur pre-dosing only ***1 hour (+/- 30 minutes) before administration of IM injection.***

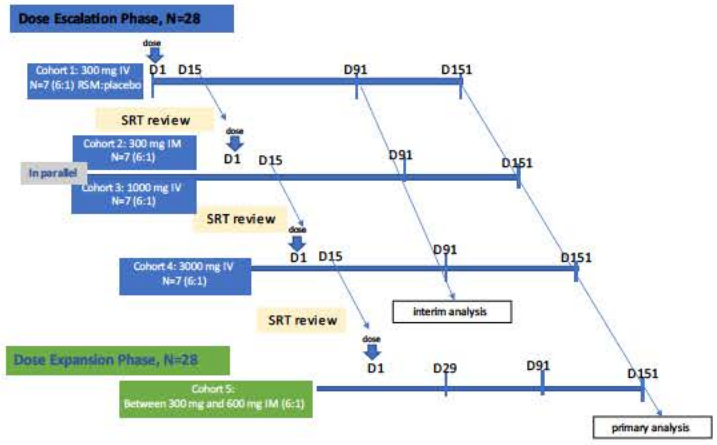
Masking: Participants and all study personnel will be blinded to the randomization, with one exception: the first sentinel participant ***in each Dose Escalation Phase cohort*** will be single-blinded (participant-blinded) and ***will*** receive the respective dose of RSM01. Authorized study site personnel will administer doses

Figure 1: Removed tag for Day 15 Cohort 5 visit then and moved arrow for interim analysis to appear below Cohort 4 instead of below Cohort 5. Removed vertical line at Day 91 for interim analysis and added a diagonal line and removed vertical line from Day 151 and added a diagonal

old version



new version



Schedule of Activities (SoA)

Table 2: Schedule of Activities for the Dose Escalation Phase (Cohorts 1-4)

Added distribute memory aid to V3 and V4 and collect memory aid to V4 and V5 for Table 2 and distribute to V1 and collect to V8 for Table 3

Table 2: Schedule of Activities for the Dose Escalation Phase (Cohorts 1-4)

Visits	Screen	Pre-V1	V1	V2	V3	V4	V5
Distribute memory aid					*X*	*X*	X
Collect memory aid						*X*	*X*

Table 3: Schedule of Activities for the Expansion Phase (Cohort 5)

Visits	Screen	Pre-V1	V1	V2
Distribute memory aid			***X***	X
Collect memory aid				***X***

Added an X for pregnancy test and vital signs, for discontinuation visit for both Table 2 and Table 3

Visits	Discon
Study Day and Visit window days (d)	**Visit**
Activities:	
Serum pregnancy test[2]	***X***
Vital signs	***X***

Table 2 Footnote 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, after end of infusion for IV doses and at 8-hours (±0.5 hour) and 24-hours (±1 hour) after IM doses*** ~~post dose for both IV and 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.***

Table 3 Footnote 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.***

Section 2.1 RSV and Burden of Disease

RSV is the most common pathogen identified in young children with acute LRTI. Most children ***acquire*** ~~get~~ an RSV infection by the time they are 2 years old, causing a mild, cold-like illness within 4 to 6 days after infection. However, in some children it leads to a more severe illness such as bronchiolitis and~~/~~pneumonia and may also increase the~~ir~~ risk of developing subsequent asthma and/or recurrent wheezing episodes in early childhood.

Section 2.3 RSM01 mAb Candidate

RSM01(***also designated as*** ~~aka~~ ADI-15618-IVNS YTE)

Section 2.3.1 Non-Clinical Development of RSM01

In summary, there were no test-article related target organ~~s of~~ toxicit***ies***~~y~~, no effects on vital systems,

Section 2.5.1 Edited text:

Th~~o~~***e***se projection***s*** suggest that following ~~an~~ RSM01 doses ~~of~~ ≥300 mg ~~is predicted~~ the RSM01 concentration is predicted to be above the target EC90 threshold at Day 151.

Section 2.5.2: Edited text:

Final selection of the dose ***to be*** administered to Cohort 5 will be made by the sponsor and informed by available RSM01 PK data, as well as relevant safety data, from the Dose Escalation Phase.

Available interim ~~Any available~~ PK data from ***the Dose Escalation Phase cohorts*** ~~from earlier s~~***, combined with published data from previous studies of monoclonal antibodies,*** will be used to develop a population PK model to describe the individual concentration time profiles ***of RSM01.*** Subsequently, the model will be used in a simulation mode to predict the proportion of participants that are expected to ***have RSM01 concentrations*** ~~be~~ above the EC90 on Day 151**.**

The tentatively determined dose to be tested in the ***Dose*** Expansion Phase cohort is ~~between~~ ≥300 mg and ≤600 mg IM**,** based on…

Section 2.6 Benefit/Risk Assessment

However, ***it is*** ~~we~~ expect***ed*** that RSM01 will have a similar benefit/risk profile to nirsevimab.

A Phase 1 FiH study in adults in the U.S. evaluated a single dose of nirsevimab or Placebo administered as an IV dose of 300mg, 1000mg, or 3000mg or as an IM dose of 100mg or 300mg [Griffin, 2017] ***and*** did not have any study discontinuations due to AEs or SAEs. The most frequently reported nirsevimab-related AEs were headaches (all mild), occurring in 3 (2.9%) ***participants.***

There were no anaphylaxis or other notable hypersensitivity reactions. In the nirsevimab group, 4 ***infants experienced*** ~~cases~~ ~~reported~~ rash. One ***infant experienced*** ~~case~~ ~~reported~~ one day of petechiae occurring 4 months after nirsevimab, which was not assessed by a health care provider. All 3 AESI ***infants*** ~~cases~~ in the Placebo group had rash.

In the nirsevimab Phase 1b/2a infant trial~~:~~ ***none*** no one had ADA at baseline and only the mAb group…

The Phase 1 MK-1654 study randomized 152 healthy adults ***in a*** ~~at~~ 3:1 ratio

RSV Mutations

Escape mutant selection studies ***with RSM01*** were performed…

… have largely comparable neutralization potency ***based on*** in vitro and in vivo virus neutralization assays…

In vitro cell-based neutralization studies showed that RSM01 performed better than other RSV ***monoclonal antibodies*** palivizumab

General Risks with MAb Infusion

Administration of any mAb may carry a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies against the mAb~~.; h~~***H***owever, these reactions are …. In this regard, as RSM01 is targeted to a viral antigen, ~~and~~ is a fully human mAb (IgG1), ***and it*** is expected to have …

Section 4.1 Study Design Overview

Dose Escalation Phase, continued:

After the 24-hour post-dose period for the sentinel participant in each Dose Escalation Phase cohort, ~~On any given day, each~~ participant***s*** in the Dose Escalation Phase cohorts should be dosed at least 2 hours apart regardless of ***route*** ~~mode~~ of…

Each dose escalation step will proceed after ***all participants in*** the prior cohort ha***ve***~~s~~ completed Day 15, and the SRT has reviewed the data and determined that ***a pausing rule has not been met*** ~~that no pausing event has occurred~~ ~~that no pausing event has occurred.~~

Dose Expansion Phase:

Enrollment in the Dose Expansion Phase (Cohort 5) will begin after Day 15 for participants in Cohort 4, and after the SRT has reviewed the data and determined that ***a pausing rule has not been met.***

Th~~os~~e predictions …

Section 5.1 Inclusion Criteria: ***(***inclusive***)***

Sex

4. Both males and females are eligible to participate.

Male participants with partners of childbearing potential must agree to use condoms during their participation in the study and for 90 days after the participant completes the study. Male participants must also agree to refrain from sperm donation for at least 90 days after they complete the study.

Female participants of childbearing potential must not be pregnant, breastfeeding, or attempting to become pregnant for 28 days before Screening and throughout the duration of their participation in the study. These participants must have a negative serum pregnancy test at Screening in order to be eligible for randomization and treatment with study intervention. In addition, female participants must be willing to commit to using a consistent and acceptable method of contraception for the duration of their participation in the study and for 90 days after they complete the study if they engage in intercourse. Acceptable methods of contraception are:

- ***Consistent use of systemic contraception, including birth control pills, transdermal patch, vaginal ring, implants, and injectables.***
- ***Consistent use of double barrier method, e.g., condoms, cervical cap, diaphragm, vaginal contraceptive film with spermicide.***
- ***Use of intrauterine device with a low failure rate (defined as < 1% risk of pregnancy per year)***
- ***Monogamous intercourse with a vasectomized man or has only same-sex partners.***

Female participants who are not sexually active but become so during the study must agree to follow the contraceptive requirements above.

Female participants who are not of childbearing potential must meet at least one of the following criteria:

- ***At least 1 year since the last menstrual period.***
- ***Surgically sterile (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy)***
- ***Congenitally sterile***
- ***Diagnosed as infertile and not undergoing treatment to reverse infertility.***

~~For female participants: not pregnant and agree to avoid pregnancy throughout the study. For male participants who have a female partner of childbearing potential or a pregnant partner: condom use for the duration of the study period (approximately 5 months).~~

~~Women physically capable of pregnancy must agree to use an acceptable method of avoiding pregnancy during the study. Acceptable methods of avoiding pregnancy include sexual abstinence (not engaging in sexual intercourse), a confirmed sterile partner, or at least 2 contraception methods from the following list: male or female condom, diaphragm, intrauterine devices (IUDs), hormonal contraceptive (oral, injection, transdermal patch, or implant). Adequate contraception does not apply to participants of childbearing potential with same-sex partners, when this is their preferred and usual lifestyle.~~

Additional Requirements: Participants ***must*** ~~who …~~

Section 4.2 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study ***or conduct of the*** last scheduled procedure shown in the SoA for the last participant in the trial.

Section 5.2 Exclusion Criteria: restarted numbering at 1 (previously started at 7) and renumbered after adding new criteria.

Prior Concomitant Therapy: added the following criterion

Added ***7. Having received any vaccination (including COVID-19 vaccine) within the 15 days before Day 1, or planning to receive a dose of any vaccine during the 15-day period following Day 1.***

Prior/Concurrent Clinical Study Experience

Added: ***13. Previously having participated and received study intervention in the current study.***

Section 6. Study Intervention

Table 5

Dosage, Volume and Route of Administration	300mg ***(53mL***) ~~(50mL) per~~ IV infusion 1000mg ***(60mL)*** ~~(50mL) per~~ IV infusion 3000mg ***(130mL)*** (~~100mL) per~~ IV infusion 300mg ***(3mL)*** IM injection (1 injection ~~of 3mL~~ in the anterolateral thigh muscle)	Same volume and number of infusions/injections as the RSM01 group.
Dose **Expansion Phase Cohort**		

Section 6.1 RSM01 Drug Product

Deleted ~~Vials with visible particles at the end of the thaw procedure should not be used.~~ ***Refer to Pharmacy manual for details.***

Section 6.2 Placebo Drug Product

Each vial contains an isotonic, sterile solution that is a colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. Refer to Pharmacy manual for details.

Section 6.3 Study Intervention Preparation and Administration

For the Dose Escalation Phase, the first (sentinel) participant undergoing study intervention administration in each cohort will ***receive*** ~~be in the~~ RSM01 ~~arm~~. The next participant in each cohort can be dosed at least 24 hours after the sentinel participant. ***After the 24-hour post-dose period for the sentinel participant in each Dose Escalation Phase cohort*** ~~On any given day,~~ participants in the Dose Escalation Phase ~~only~~ should be dosed at least 2 hours apart regardless of ***route*** ~~mode~~ of administration (IM or IV). The ≥2-hour wait time between IV infusions is to begin at the end of the previous ***participant's*** infusion. ***The ≥2-hour wait time between IM injections is to begin at the time of the previous participant's IM injection.***

Section 6.3.1 IM Injection

For IM dosing in the Dose Escalation Phase, participants in ***Cohort 2*** ~~the 300mg Cohort~~ will…

The Dose Expansion Phase cohort may receive ***RSM01 (≥300mg to ≤ 600mg) or Placebo*** ~~up to 600mg IM of RSM01~~ in the anterolateral thigh muscle. If more than ***3 mL of study intervention*** ~~300mg~~ is administered in a single dose, the volume and number of injections will be adapted…

Section 6.3.2 IV Infusion

The total IV infusion volume will be ***53mL for Cohort 1, 60 mL for Cohort 3, and 130mL for Cohort 4.*** ~~50mL for the 300mg cohort and the 1,000mg cohort, and 100mL for the 3,000mg~~

~~cohort~~ The IV infusion time will be approximately 2 hours or less depending on the cohort. The ≥2-hour wait time between administration of IV infusions to successive participants is to begin at the end of the previous ***participant's*** infusion.

Section 6.4. Handling/Storage/Accountability

The study intervention (RSM01 ***and*** ~~and~~ Placebo) must be stored at 2°C to 8°C in a secure~~d~~ location with no access for unauthorized personnel.

~~At the end of the study, u~~ ***U***nused supplies will be destroyed…

Section 6.5.1. Randomization

The remaining 6 participants in each ***Dose Escalation Phase*** cohort (Cohorts 1, 2, 3 and 4) will be…

Section 6.5.2 Masking

Deleted duplicate text ~~The first sentinel participant in each of the Dose Escalation Phase cohorts will each receive the respective dose of RSM01 in a single-blind fashion: participants will be observer-blind (the study personnel will know their study assignment).~~

Section 6.7 Concomitant Therapy

anti-inflammatory drug~~s and~~**,** antipyretic drug, or…

A COVID-19 vaccination ***may be received by a participant during the study but not within the 15 days immediately following administration of the study intervention.*** ~~Note that any planned COVID-19 vaccination may be given, but it is recommended to defer vaccination until at least 7 days following study intervention administration~~

Section 6.8 Dose Modification

This is a dose escalation and ***dose*** expansion study. Refer to Section 3 for details regarding ***dose*** escalation and ***dose*** expansion

Section 7.1.1. Pausing Rules

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 toxicity 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 and the U.S. FDA will be notified in an expedited manner.

Refer to Section 8.2.6 for the role of SRT and Section 8.2.7 for the role of the IDMC.

If the investigator and/or the SRT observes that a pausing rule is met, the investigator will inform the sponsor and/or the SRT as soon as possible and within 24 hours of the observation. The SRT and/or sponsor will notify the investigator and the IDMC members of the pause in enrollment and participant dosing as soon as possible and within 24 hours of receiving notification of the pausing rule being met.

When a pausing rule is met, the IDMC members will convene an urgent ad hoc review meeting, review all relevant unblinded safety data, and make a recommendation to the sponsor. The FDA will be advised of the IDMC actions and recommendations.

The IDMC may recommend continuation of the study pause or resumption of enrollment and dosing with or without changes to the protocol. The final decision to pause or resume study activities will always be the responsibility of the sponsor. All IDMC recommendations will be stored according to the IDMC Charter.

All sponsor decisions will be documented in a memorandum to the study file. The sponsor or delegate is responsible for prompt communication to the study site of decisions related to pausing or resuming the study activities, including notification to the investigator, relevant IRBs/IECs and regulatory authorities.

The clinical site will be allowed to resume activities only upon receipt of written notification from the sponsor.

~~***If an investigator observes that a pausing rule is met***, the investigator will inform the sponsor or delegate as soon as possible and within 24 hours of the observation. The sponsor or delegate will notify the investigator and the IDMC members of the pause in enrollment and participant dosing as soon as possible and within 24 hours of receiving notification of the condition being met.~~

~~The IDMC members will review all relevant safety data, convene an urgent ad hoc review meeting and make a recommendation to the sponsor with regards to maintaining the pause or resuming enrollment/participant dosing.~~

~~***If the SRT observes that a pausing rule is met***, the SRT will inform the sponsor and the IDMC as soon as possible and within 24 hours of the identification of the condition being met.~~

~~The SRT will notify the study investigator of the pause in enrollment and dosing as soon as possible and within 24 hours of the observation.~~

~~***If the sponsor or delegate observes that a pausing rule is met***, the sponsor will notify the study investigator and the IDMC of the pause in enrollment and dosing as soon as possible and within 24 hours. The IDMC will review all relevant safety data, convene an urgent ad hoc review meeting and make a recommendation to the sponsor with regards to lifting or maintaining the pause in enrollment/participant dosing.~~

~~The IDMC may recommend resumption of enrollment and dosing with or without changes to the protocol. The final decision to pause or resume study activities will always be the responsibility of the sponsor. All IDMC recommendations will be stored according to the IDMC Charter.~~

~~All sponsor decisions will be documented in a memorandum to the study file. The sponsor or delegate is responsible for prompt communication to all relevant study sites of decisions related to pausing or resuming the study activities, including notification to the investigator, relevant IRBs/IECs and regulatory authorities.~~

~~The clinical sites will be allowed to resume activities only upon receipt of written notification from the sponsor.~~

Section 7.2 Participant Discontinuation or Withdrawal from the Study

At this visit, topics around participant safety as well as the use of already collected biospecimens will be discussed, and ***the*** procedures ***and specimen collection*** indicated in the SoA…

A participant who becomes pregnant during the study period will be asked to complete all visits and procedures through Day 151 as described in Table 2 or Table 3, as applicable. After she completes Day 151, or in the event that she voluntarily withdraws from the study and agrees to provide additional information regarding the pregnancy, the investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate. Neonate follow-up will occur for 6 weeks beyond the estimated delivery date (refer to Section 10.3).

Neonate follow-up will occur for 6 weeks beyond the estimated delivery date (refer to Section10.3).

~~A participant who becomes pregnant will be followed for safety as described in the protocol, without any of the protocol-required blood draws. She will be followed up during the gestation period and after the delivery to collect information on the health of the participant and the newborn. The results of the outcome of pregnancy will be captured in a 'Pregnancy Outcome Form' and the sponsor will be notified.~~

Section 7.4 COVID-19 Contingency Plans

Assure changed to ensure 3 times

At ***the*** ~~study sites~~ ***study site***

Section 8. Study Assessments and Procedures

described in Section~~s~~ 5.1 and ***Section*** 5.2, ***respectively***.

Section 8.1 Safety Assessments

All Day 1 safety assessments and sample collections are prior to ***administration of*** study intervention.

Prior to opening each of Cohorts 2, 3, and 4 to enrollment, the SRT will conduct safety assessment of data for the previous cohort collected for ***all participants*** through Day 15,

Section 8.1.1 Confinement Period and Sentinel Participants

Participants in the Dose Escalation Phase will be confined at the study site ~~after informed consent is signed,…~~

On Day -1, participants will undergo ~~a serum pregnancy test,~~ safety laboratory assessments and other screening procedures

The first participant in each of the Dose Escalation Phase cohorts will be a sentinel participant and will receive RSM01 at the respective dose of RSM01 in a ***participant-blind*** ~~an observer-blind~~ fashion.

The next participant in each cohort can be dosed at least 24 hours later~~.~~***, if there is no safety concern.***

Dose Expansion Phase

On this Day -1 ***visit***,… participants will begin confinement, and undergo ~~a serum pregnancy test,~~ safety laboratory assessments and…

Section 8.1.2

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)***,…

Section 8.1.2.1 Vital Signs

Vital sign measurements will be recorded for pulse rate, systolic and diastolic blood pressure, respiratory rate, ~~and~~ body temperature ***and percent oxygen saturation by fingertip pulse oximetry***.

Section 8.1.3 Focused Physical Examination and Medications/Vaccinations

~~A f~~***F***ocused physical examinations, will be performed ***on Day 1 and all subsequent visits, as indicated in the SoA*** ~~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.~~

Throughout the study, any concomitant medications taken, including antipyretics, and anti-inflammatories, ***and vaccinations*** will be recorded

Section 8.1.4 Pregnancy Status Assessment

A blood sample will be collected ***from female participants*** at screening and at Day -1 for serum beta human chorionic gonadotropin (βHCG) testing.

Serum βHCG testing ***of female participants*** should be performed during the study if a pregnancy is suspected.

Serum βHCG testing of female participants of childbearing potential should be performed at the discontinuation visit.

A participant who becomes pregnant during the study period will be asked to complete all visits and procedures through Day 151 as described in Table 2 or Table 3, as applicable. After she completes Day 151, or in the event that she voluntarily withdraws from the study and agrees to provide additional information regarding the pregnancy, the investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate.

Neonate follow-up will occur for 6 weeks beyond the estimated delivery date (refer to Section 10.3).

~~If a participant becomes pregnant during the study, she will be withdrawn from all study procedures going forward, i.e., blood draws and laboratory evaluations described in the SoA will not be performed once a participant is known to be pregnant. However, she will be encouraged to continue in the study for safety follow-up.~~

Section 8.1.6 Electrocardiogram, Hepatitis Screening and Urine Drug Screening

Triplicate (unmarked) 12-lead ECGs will be obtained ~~and averaged~~. For the Dose Escalation Phase, the ECGs will be taken at screening, and 24 hours post-dose, on Day 2. For the ***Dose*** Expansion Phase, the ECG***s*** will be taken at screening.

Section 8.1.7. Clinical Safety Laboratory Assessments

Clinical safety laboratory parameters that will be evaluated include:

g. Hematology: Complete blood count (hemoglobin, ***hematocrit, red blood cell count***, platelet~~s~~ ***count*** and white blood cell~~s~~ ***count***) and absolute counts for neutrophils, lymphocytes, ***eosinophils*** and monocytes

h. Serum chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, gamma glutamyl transferase (GGT), creatinine, blood urea nitrogen, ***lactate dehydrogenase (LDH),*** ~~and~~ glucose, ***albumin, sodium, potassium, chloride, bicarbonate, and calcium***

The investigator must review the laboratory report, document th***ise*** review

Section 8.1.9

Diary Card

The diary card will be collected and reviewed by the investigator (or designee) on ***the*** Day 8 Visit

Memory Aid

A memory aid will be utilized by participants to collect unsolicited AEs beginning at discharge from the clinic, through Day 151 (end of study participation). Participants will be instructed to record unsolicited AEs whenever they occur, recording such AEs on the memory aid.

~~A memory aid will be distributed to the participant on the Day 8 visit and at each subsequent visit through Day 121 for Dose Escalation Phase cohorts and through Day 91 for the Expansion Phase cohort. Participants will be instructed to record unsolicited AEs whenever they occur, using the aid.~~

Section 8.2 Adverse Events and Serious Adverse Events

Site staff will document ***any AEs*** in the study

Solicited AEs that continue beyond Day 7 will be captured in ***the*** unsolicited AEs memory…

Immediate safety concerns should be discussed with the sponsor, and the SRT. The SRT will trigger an IDMC review if any pausing ***rule is met*** ~~event occurs~~

Clinical ~~Bio~~chemistry and/or hematology ***results*** ~~findings~~ may also qualify as AEs ***(Section 10.4, Appendix 4).*** ~~if the investigator considers them as such.~~

However only the investigator ***or sub-investigator*** ~~study physician~~ is responsible for assessment, including assignment of causality and, for unsolicited AEs, the intensity, and for reporting and management of all AEs. The investigator is responsible for following up all AEs regardless of their relatedness to study intervention or study procedures, or AEs that caused the participant to ***withdraw from*** ~~discontinue~~ the study…

Medical History/Current Medical Conditions section of the CRF, not ***in*** the AE section.

Investigators are not obligated to actively seek AEs, SAEs or AESIs after ***a participant concludes*** ~~conclusion of~~ study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be related to the study intervention or study participation, the investigator must notify the sponsor or designee within ~~the same~~ 24 hours. ~~timeline.~~

Section 8.2.3.1 AE Intensity

The intensity of AEs will be classified by the investigator based on the toxicity grading tables (Section 10.4 10.4 Appendix 4). In the case of an AE or abnormal clinical laboratory result not included in Appendix 4, intensity will be assigned using the Grades described in the U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events, Version 5.0 [US HSS 2017] (See Section 10.2.5.1.)

Local solicited AEs will be recorded on the diary card by the participant and graded and/or measured by the participant. An exception is that the study investigators will grade solicited AEs during the confinement period. Any participant-reported Grade 3 or higher adverse event will be assessed by the investigator.

~~Unsolicited AEs will be classified by the investigator as mild (Grade 1, not interfering with normal daily activities), moderate (Grade 2, interfering with normal daily activities), severe (Grade 3, preventing normal daily activities) or potentially life-threatening (Grade 4). Refer to Appendix 2, Section 10.2.5.1 and Section 10.4 for toxicity grading tables. Local solicited AEs will be recorded on the diary card by the participant and either graded and/or measured by the participant. An exception is that the study investigators will grade solicited AEs during the confinement period for the Dose Escalation Phase.~~

Section 8.2.3.2 AE Causality/Relationship to Study Intervention

All AEs will be evaluated by the investigator or medically qualified designee (i.e., investigator, ***sub-investigator*** ~~study physician~~) to ***assess*** ~~characterize~~ the relationship between study intervention and ***the*** AE…

The causality will be assessed as ***either*** related…

the Medical Monitor ***or*** ~~and~~ sponsor designee

The sponsor or designee will never downgrade a case from serious to non-serious ***or change the investigator assessment of causality from related to not related.***

Any participant-reported Grade 3 or higher adverse event will be assessed by the investigator.

Section 8.2.6 Safety Review Team

Meetings of the SRT to decide on proceeding to each subsequent cohort will occur when all participants in the current cohort have completed Day 15. The SRT will also meet approximately every 8 weeks during the Dose Expansion Phase. The SRT will review all available blinded safety data collected at the time of the review to determine whether or not any pausing event has occurred (See Section 7.1.1.). If a pausing event does not occur, dose escalation or moving to the Dose Expansion Phase cohort can occur.

If a pausing rule is met, the SRT will ask the IDMC to conduct a review of unblinded safety data. The IDMC will make a recommendation to the sponsor regarding the further conduct of the study.

~~Meetings to decide on proceeding to each subsequent cohort will occur when the current cohort completes Day 15. The SRT will review all available safety data collected at the time of the review to determine whether or not any pausing event occurs that would trigger an IDMC review. If a pausing event does not occur, dose escalation or moving to the Dose Expansion Phase cohort can occur.~~

~~An ad hoc SRT meeting will occur immediately if any Grade 3 or higher AE, or SAE, or AESI, is reported, regardless of relationship to the study intervention. If the event is determined to be study intervention-related, the IDMC review will be triggered, and pausing will occur with enrollment and further dosing, until after the IDMC review.~~

Section 8.2.7 Independent Data Monitoring Committee

The IDMC will operate according to a charter ***approved by the sponsor and all IDMC members***. The IDMC structure, participants, and other details will be provided in the charter. The charter will be ***approved*** prior to ***enrollment of the first study participant***.

The role of the IDMC will be to (a) monitor the progress of the study, (b) review blinded safety data provided by the SRT, (c) review unblinded safety data if a pausing rule is met, and (d) make recommendations to the sponsor on further conduct of the study if a pausing rule is met. ~~review unblinded safety data and make recommendations if events necessitating a pause in enrollment and in participant dosing occur. Refer to Section 7.1.1 for pausing rules.~~

~~If a pausing rule is met, the IDMC may request additional information.~~

~~The IDMC will make a formal recommendation to the sponsor on the continued enrollment into the trial if a pausing rule was met. Immediate safety concerns should be discussed among sponsor representatives and the SRT, and if needed the IDMC.~~

~~If RSM01administration is paused by the Medical Monitor or the investigator, the IDMC will convene on an ad hoc basis.~~

The recommendations of the IDMC, along with the sponsor's decision, will be communicated to ***the investigator, to the responsible IRBs/IECs and to the US FDA***. ~~the investigators and the IRBs/IECs and the national regulatory authorities as required. The sponsor or its designee agrees to abide by any directives issued by the national regulatory authority or the IRB/IEC.~~

Section 8.3. Treatment of Overdose

If ***an overdose*** ~~it~~ were to occur, the overdose, including misuse or abuse of the product and medication errors, …

Section 8.4 Blood Sampling

Whole blood samples will be collected for measurement of PK, **ADA,** and RSV

8.,5 Pharmacokinetics

Dose Escalation Phase: ***At Visit 1, PK blood draw will occur pre-dosing, 1 hour (+/- 30 minutes) before administration of IM injection or beginning of infusion, for all participants in Cohorts 1-4. For participants who receive IV study intervention, the timing of post-dose blood samples begins at the end of the IV infusion. Samples are obtained at 5 minutes (± 1 minute) at 8-hours (± 0.5 hour) and at 24-hours (± 1 hour) after the end of the infusion. For participants who receive IM study intervention, the timing of post-dose blood samples begins at the time of the IM injection and samples are obtained at 8-hours (± 0.5 hour) and at 24-hours (± 1 hour) after the IM injection.***

Dose Expansion Phase: ***At Visit 1, only a pre-dose sample collected 1 hour (+/- 30 minutes) before administration of IM injection*** is obtained at Day 1.

is obtained at Day 1.

Blood for PK samples at all visits after Day 1 will be obtained according to the SoA as shown in Table 2 and Table 3.

~~**Dose Escalation Phase:** At Visit 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) and 24 hours (± 1 hours) post-dose for both IV and IM doses.~~

~~**Dose Expansion Phase:** Blood samples **at Day 1** will be drawn at pre-dose only.~~

Remaining samples collected for analyses of RSM01 may also be used to evaluate immunogenicity and***/or*** safety aspects ~~or efficacy aspects~~ related to ***any*** concerns arising during or after the study.

Section 8.6 Pharmacodynamics

Whole blood samples in serum separator tubes and VAMS ***devices*** will be

Remaining samples collected for analyses of RSV neutralization may also be used to evaluate drug concentration, immunogenicity, and safety ~~or efficacy~~ aspects

Section 9.1 Sample Size Determination

This trial is an exploratory trial to characterize safety, tolerability***,*** and pharmacokinetics of single dose***s*** of RSM01 mAb.

Section 9.2 Populations for Analyses

Table 6

~~Modified~~ ***I***ntention to treat (~~m~~ITT) PK population

Participants will be analyzed according to the intervention ~~they~~ actually received.

Section 9.3 Statistical Analyses

A detailed statistical analysis plan (SAP) centered on primary and secondary endpoints will be developed and finalized prior to unblinding ***the study*** and will further

Section 9.3.1 Safety Primary Endpoints

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

For participants with more than 1 episode of the same event, the ***AE with*** maximum severity will be used for tabulations.

All unsolicited AEs, serious adverse events (SAEs), ***and/or*** AESI will be recorded from screening through Day 151.

…Preferred Term (PT) and ***greatest*** ~~highest~~ intensity.

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/or*** one or more AESI from screening through Day 151 will be summarized

For participants with more than 1 episode of the same event, the ***AE with*** maximum intensity will be used for tabulations.

Section 9.7 Interim Analysis

Although the sponsor will be blinded throughout the study, such review of aggregated data could potentially lead to unblinding of ***the treatment received by*** individual~~s~~ ***participants***.

Section 10.1.4.1 Informed Consent Forms

If a participant cannot be randomized on the intended day of dosing (e.g., ***due to*** ~~if~~ elevated temperature)

Section 10.2.4 Definition of AESI

The following AEs will be collected and reported as AESIs: anaphylaxis or hypersensitivity reactions, and***/or*** infusion reactions resulting in permanent discontinuation ***of study intervention infusion during IV administration.*** ~~of a participant who receives an IV dose of the study intervention~~

Section 10.2.5 Recording and Follow-Up of AE, SAE, AESI

There may be instances when copies of medical records for certain cases are requested by the Medical Monitor, ***the SRT***, the IDMC ***and/***or the sponsor.

The investigator will ~~then~~ record all relevant AE/SAE***/AESI*** information in the CRF.

There may be instances when copies of medical records for certain cases are requested by the Medical Monitor, ***the SRT,*** the IDMC ***and/***or the sponsor.

Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE***/AESI***.

Note that local AEs reported within the first 7 days after ***IM*** dosing are considered to be study intervention-related.

Follow-up and Resolution

The onset and resolution dates of the event and medical care ***provided*** ~~taken~~ in response to the event will be documented.

Section 10.2.5.1 Assessment of Intensity

The investigator will assess the intensity of each AE reported during the study. In the case of local reactions, vital signs, systemic events, and laboratory abnormalities, the Grades delineated in Section 10.4, Appendix 4 will be employed.

In the case of an AE or abnormal clinical laboratory result not included in Appendix 4, intensity will be assigned using the Grades described in the U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events, Version 5.0 [USHSS HSS 2017] as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**symptoms, causing inability to perform usual social and functional activities with intervention or hospitalization indicated

Grade 4 Life-threatening consequences; urgent intervention indicated

A semi-colon indicates 'or' within the description of the grade.

Notes:

****Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.***

Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

~~The investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of 4 categories, as defined in Appendix 4, Section 10.4~~

~~**Grade 1 Mild** symptoms, causing no or minimal interference with usual social and functional activities with intervention not indicated~~

~~**Grade 2 Moderate** symptoms, causing greater than minimal interference with usual social and functional activities with intervention indicated~~

~~**Grade 3 Severe** symptoms, causing inability to perform usual social and functional activities with intervention or hospitalization indicated~~

~~**Grade 4 Potentially life-threatening** symptoms, causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death~~

~~An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.~~

Section 10.2.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements ***applicable to SAEs***.

Section 10.2.5.4. Assessment of Outcome

The outcome of each SAE/AESI must be reported ~~to the sponsor~~.

Section 10.2.6 SAEs, AESIs, and Serious ADR Reporting

Reporting to Sponsor~~'s or~~ Delegate~~'s (CRO Safety Team)~~ Via the Electronic Data Collection Tool

Serious ADRs are reported to the sponsor ***or delegate during*** ~~and to the CRO Safety Team~~ for the entire study period. Serious ADRs are ***to be reported after completion of the study, if the investigator becomes aware of a serious ADR***. ~~even after the trial is over, if the sponsor, Medical Monitor or investigator become aware of them~~

The investigator must not wait to collect additional information to fully document the event before notifying ~~the CRO Safety Team of an~~ ***the sponsor or delegate of a***-SAE or ***an*** AESI.

- SAE***/AESI*** term and date of event onset

Contacts for SAE***/AESI*** reporting and for all safety personnel

Reporting via Paper CRF

If the eCRF cannot be completed, the Supplemental SAE/AESI Report (paper form) should be completed by the investigator or his/her designee, and scanned and emailed, or faxed to the ***sponsor or delegate.*** ~~CRO Safety Team.~~

Other Events Requiring Immediate Reporting

The investigator must report the following events by scanning and emailing, or faxing the appropriate form to the ***sponsor or delegate*** ~~CRO Safety Team~~ within 24 hours of becoming aware of the event:

Section 10.3 Appendix 3 Contraceptive Guidance and Collection of Pregnancy Information

Contraceptive Guidance:

Male participants with partners of childbearing potential must agree to use condoms during the study and for 90 days after the study, and they must refrain from sperm donation for at least 90 days after the end of study.

Female participants of childbearing potential must not be pregnant, breastfeeding, or attempting to become pregnant for 28 days before Screening and throughout the duration of the study. These participants must have a negative serum pregnancy test at Screening in order to be eligible for randomization and treatment with study intervention. In addition, these female participants must be willing to commit to using a consistent and acceptable method of contraception for the duration of the study and for 90 days after study completion if they engage in intercourse. Acceptable methods of contraception are:

- ***Consistent use of systemic contraception, including birth control pills, transdermal patch, vaginal ring, implants, and injectables.***
- ***Consistent use of double barrier method, e.g., condoms, cervical cap, diaphragm, vaginal contraceptive film with spermicide.***
- ***Use of intrauterine device with a low failure rate (defined as < 1% risk of pregnancy per year)***
- ***Monogamous intercourse with a vasectomized man or has only same-sex partners.***

Female participants who are not sexually active but become so during the study must agree to follow the contraceptive requirements above.

Female participants who are not of childbearing potential must meet at least one of the following criteria:

- ***At least 1 year since the last menstrual period.***
- ***Surgically sterile (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy)***
- ***Congenitally sterile***
- ***Diagnosed as infertile and not undergoing treatment to reverse infertility.***

Collection of Pregnancy Information:

- ***If a participant is determined to be pregnant during the study (after receiving a dose of the study intervention), the investigator will report the pregnancy to the sponsor or delegate and collect follow-up information on the participant and the neonate. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.***

- ***While pregnancy is not considered to be an AE or a SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or a SAE. Any abnormal pregnancy outcome that comes to the attention of the investigator (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) is considered to be a SAE.***
- ***Any pregnancy-related SAE that occurs after study participation and is made known to the investigator and is assessed as related to the study intervention will be reported to the sponsor or the sponsor's designee. The investigator is not obligated to actively seek such information in former study participants who become pregnant during the study.***

~~**Contraception Guidance:**~~

~~Women physically capable of pregnancy must agree to use an acceptable method of avoiding pregnancy for one year after study intervention.~~

~~Acceptable methods of avoiding pregnancy include at least one of the following:~~

- ~~sexual abstinence (not engaging in sexual intercourse)~~
- ~~a confirmed sterile partner~~
- ~~use of at least 2 of the contraceptive methods shown below:~~
    - ~~hormonal contraceptives (oral, injection, transdermal patch, or implant)~~
    - ~~IUD~~
    - ~~male or female condom~~
    - ~~diaphragm.~~

~~Adequate contraception does not apply to participants of childbearing potential with same-sex partners, when this is their preferred and usual lifestyle.~~

~~i. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.~~

~~j. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.~~

- ~~Any pregnancy-related SAE that occurs after study participation and is made known to the investigator and is assessed as related to the study intervention will be reported to the sponsor or the sponsor's designee. The investigator~~ is not obligated to actively seek this information in former study participants.

Section 10.4 Appendix 4: Toxicity Tables

The following toxicity tables are extracted from the FDA Guidance ***for*** ~~to the~~ Industry

Notes to Table 9:

** "ULN" ~~–~~ is the upper limit of the normal range.

GGT grading is not provided in the FDA toxicity grading scale tables. The following grading scale is from the U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events, ***Version 5.0*** [US HSS 2017]:

Other:

eg changed to e.g.

ie changed to i.e.

added missing comma's where applicable

corrected minor spelling errors

updated table of content

updated first use of abbreviation as appropriate

changed subject to participant throughout

Version 3.0, dated 10 December 2021

Rationale for v3.0 (changes to v2, 20 July 2021): The update from v2 to v3, was prepared to define the responsibilities of the Safety Review Team, the sponsor Chief Medical Officer, and the Independent Data Monitoring Committee.

Other minor changes were made for correction or clarification. All changes are provided below. New text is shown in bold italics and old text is shown with strikethroughs.

Synopsis

Safety Review Team: A SRT will be established as the team responsible for ***recommending dose escalation or dose expansion to the sponsor's Chief Medical Officer*** ~~dose escalation decisions and proceeding to dose expansion~~.

Meetings ***of the SRT to provide a recommendation on dose escalation or dose expansion will occur during the Dose Escalation Phase when all participants in the currently dosed cohort have completed Day 15***~~to decide on proceeding to each subsequent dose escalation cohort will occur when all participants in the current cohort complete Day 15.~~

Schedule of Activities, Table 2 continued.

A correction was made to the visit window for Day 3 Visit 3 in the table header on the second page of the table to align with the table header on the first page of the table. The window was corrected to ±0 days.

V3
D3 ±***0***~~1~~d

Section 8.1 Safety Assessments

Prior to opening ~~each of~~ Cohorts ~~2,~~ ~~3 and 4~~ 2 ***and*** 3 *together*, ***Cohort*** 4, ***and Cohort 5, respectively,*** to enrollment, the SRT will conduct ***a*** safety assessment of data for the previous cohort***/s*** collected ~~for~~ w***hen*** all participants ***in the currently dosed cohort have completed*** Day 15.~~, following the study intervention~~.

Section 8.2.6 Safety Review Team

A SRT will be established as the team responsible for ***recommending*** dose escalation ***or*** ~~decisions and decision on proceeding to~~ dose expansion ***to the sponsor's Chief Medical Officer. The SRT will operate according to the Safety Review Team Plan.***

Meetings of the SRT ***to provide a recommendation on dose escalation or dose expansion*** ~~decide on proceeding to each subsequent cohort~~ will occur ***during the Dose Escalation Phase*** when all participants in the current***ly dosed*** cohort have completed Day 15.

If a pausing event does not occur, dose escalation or moving to the Dose Expansion Phase cohort ***will be recommended by the SRT*** ~~can occur~~.

If a pausing rule is met, the SRT will ask the IDMC to conduct a review of unblinded safety data. The IDMC will make a recommendation to the sponsor regarding the further conduct of the study ***(See Section 8.2.7.)***.

~~The SRT will consist of a panel of at least 4 members, including the Gates MRI clinical lead, the Gates MRI safety lead, the study Medical Monitor, and the site principal investigator. The SRT members are part of the study team and will review blinded safety data.~~

Section 8.2.7 Independent Data Monitoring Committee

The role of the IDMC will be to (a)***-review unblinded safety data if a pausing rule is met*** ~~monitor the progress of the study, (b) review blinded safety data provided by the SRT, (c) review unblinded safety data if a pausing rule is met,~~ and (***b~~d~~***) make recommendations to the sponsor on further conduct of the study if a pausing rule is met.

Section 10.2.6 SAEs, AESIs, and Serious ADR Reporting

~~**Other Events Requiring Immediate Reporting**~~
~~The investigator must report the following events by scanning and emailing, or faxing the appropriate form to the sponsor or delegate within 24 hours of becoming aware of the event:~~ ~~Withdrawal of consent during the study for medical reasons (Immediately Reportable Event Form)~~ ~~Emergency unblinding (Immediately Reportable Event Form)~~ ~~Protocol violation affecting the safety of a participant or involving the study intervention administration process (Immediately Reportable Event Form)~~ ~~Any event that, in the opinion of the investigator, precludes further administration of the study intervention (Immediately Reportable Event Form, unless meets SAE criteria)~~ ~~Pregnancy (Immediately Reportable Event Form, and Pregnancy Notification Form)~~

Version 4.0, dated 21 January 2022

Rationale for v4.0 (changes to v3, 10 December 2021): After the study site provided information that a large proportion of screening failures has been due to inability to meet the body mass index (BMI) requirement, the sponsor agreed to raise the BMI eligibility inclusion criterion to reflect real world conditions, without affecting the safety of potential participants. The CDC criterion for obesity is a BMI>30; therefore, the updated inclusion criterion kept the BMI below this value. In addition, text was clarified for the exclusion criterion regarding timing of screening relative to a previous investigational drug.

The text regarding screening failures was modified after approximately 30% of screen failures in Cohort 1 did not meet the BMI eligibility requirement. Therefore, participants previously excluded due to BMI ≥25 kg/m2 may be rescreened once, under this amendment. Participants who also initially failed screening for other reasons may also be rescreened once.

All changes are provided below. New text is shown in bold italics and old text is shown with strikethroughs.

Section 5.1 Inclusion Criteria

Weight

3. Body mass index (BMI) 18 to ~~24.9~~ ***29.9*** kg/m2 (inclusive)

Section 5.2 Inclusion Criteria

Prior/Concurrent Clinical Study Experience

11. Participation in an interventional clinical trial and/or receipt of any investigational drug within ***30*** ~~90~~ days ***or 5 half-lives of the investigational drug before the first day of study drug dosing in this study, whichever is longer*** ~~prior to administration of study drug on Day 1.~~

Section 5.4 Screen Failures

Res~~S~~creening assessments ***as outlined below may be performed after obtaining informed consent*** ~~can be done at any time during the screening window (Day -30 to Day -2; SoA, Section 1.3), except for written informed consent~~, which must be completed prior to any ***re***screening procedure.

Rescreening is only permitted under one or more of the following ***scenarios*** ~~conditions~~:

- If a participant presents with an acute illness on the day of planned study intervention, e.g., elevated temperature, acute respiratory or gastrointestinal illness, or urinary tract infection (UTI), and meets all other eligibility criteria and can be rescreened within the originally defined screening window (SoA, Section 1.3). ***A new participant number is not required. If the participant is rescreened during the original screening window, obtaining a second informed consent of the participant is not required.***

- If there are technical difficulties with phlebotomy at screening (e.g., laboratory reports hemolyzed blood), technical error in running the laboratory tests or an abnormal urine analysis due to menstruation or UTI, and the participant can be rescreened within the originally defined screening window (SoA, Section 1.3). ***A new participant number is not required. If the participant is rescreened during the original screening window, obtaining a second informed consent of the participant is not required.***
- If a participant is undergoing screening and the study reaches a pausing rule. The participant may ***be*** rescreen***ed*** when and if the IDMC recommends, and the Sponsor determines, that the study may continue. ***A new participant number is not required. If the participant is rescreened during the original screening window, obtaining a second informed consent of the participant is not required.***
- ***If a participant fails to meet eligibility criteria upon initial screening, a one-time only rescreening for eligibility may be performed. In this case, the participant must receive a new participant number after signing a new informed consent.***

~~Repeat screening procedures may be performed as long as they are completed within the screening window.~~

Minor change: On title page version is represented by v instead of V for consistency with version history page and header.

Signature Page for Gates MRI-RSM01-101 Protocol Version 4.0 (21 Jan 2022) v7.0

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