TITLE PAGE

Protocol Title: A Phase 1, open-label, randomized, parallel group, single-dose clinical pharmacology study to investigate the relative bioavailability, safety, and tolerability of two different concentrations of sotrovimab administered at different injection sites, in male or female healthy participants aged 18 to 65 years.

Protocol Number: GSK Study 218128/VIR-7831-5012/Amendment 3

Compound Number or Name:	Sotrovimab (also known as Xevudy, GSK4182136, VIR-7831)

Brief Title: Relative bioavailability, safety, and tolerability of single-dose sotrovimab injection in adults

Study Phase: Phase 1

Acronym: COSMIC (**C**linical pharmacology study to investigate the relative bi**O**availability, safety, and tolerability of two different concentrations of **S**otrovi**M**ab administered at different **I**nje**C**tion sites)

Sponsor Name and Legal Registered Address:

Vir Biotechnology, Inc.
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San Francisco, CA 94158
USA

This study is sponsored by Vir Biotechnology, Inc. GlaxoSmithKline is supporting Vir Biotechnology, Inc. in the conduct of this study.

Regulatory Agency Identifying Number(s):

Registry	**ID**
IND	149315
NCT	NCT05280717

Approval Date: 30 Mar 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 3	30 Mar 2023	TMF-15739935
Amendment 2	06-SEP-2022	TMF-14575517
Amendment 1	01-FEB-2022	TMF-14439761
Original Protocol	13-DEC-2021	TMF-14082482

Amendment 3: 30 Mar 2023

This amendment is considered to be substantial based on the description of change and rationale mentioned in the below table.

Overall Rationale for the Amendment: The protocol has been amended to include the Part C safety and PK exploratory endpoints for Japanese population and to update inclusion criteria related to contraception recommendation.

Section # and Title	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.3.1 Risk Assessment Table Section 4.1: Overall Design Section 6.1 Study Intervention(s) Administered table	Added the infusion time to administer single dose of IV sotrovimab in Part C Cohort 1 Updated text in hypersensitivity reactions table to include Part C infusion time, and made minor editorial changes to explain infusion time and dose for Part C Cohort 2 will be added at the time of decision made based on safety review of Cohort 1 Updated the study intervention administered table with infusion time of 60 minutes for Part C Cohort 1	To characterize the safety and tolerability of IV sotrovimab and to potentially explore further IV doses of sotrovimab and/or alternative infusion time, the proposed range of infusion time was chosen to support clinical doses for potential future clinical studies
Section 3: Objectives and Endpoints	CCI [redacted]	New information available
Section 5.1 Inclusion Criteria	Updated IC related to contraception recommendation to include the reference to 5 half-lives of sotrovimab (and removed mention of 35 weeks time period) to align with current IB	Updated contraception follow-up period to only refer to ~5 half-lives (the equivalent follow-up that this represents is detailed in the ICF)
Section 9.2: Analysis Set	Added the definition of Enrolled criteria for Part C participants	New information available on Enrolled analysis set as Part C is not randomized
Section 9.3.1: General Considerations	Removed reference to Japanese population analysis only being conducted if data permits	CCI [redacted]
Section 9.4: Interim Analysis	Removed reference to the wording regarding the pausing of Part C Cohort 1 recruitment at time of interim	Alignment with operational strategy
Appendix 9: Protocol Amendment History	Minor editorial updates made to the statement describing substantial protocol changes and also to the summary of changes table	Updates are made for better clarity and to maintain consistency

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, open-label, randomized, parallel group, single-dose clinical pharmacology study to investigate the relative bioavailability, safety, and tolerability of two different concentrations of sotrovimab administered at different injection sites, in male or female healthy participants aged 18 to 65 years.

Brief Title: Relative bioavailability, safety, and tolerability of single-dose sotrovimab injection in adults

Rationale:

There is a significant unmet need for additional therapeutics to reduce COVID-19 infection; reduce the progression of mild to severe disease; treat severe disease in these patients; and to help alleviate the burden on healthcare systems.

As the COVID-19 pandemic continues to evolve with the rapid evolution of VOI/VOCs, healthcare professionals treating COVID-19 infections will need to identify the best treatment for their patient based on the circulating variants and underlying comorbidities.

Sotrovimab is being developed for treatment of COVID-19. Sotrovimab is a human IgG1κ mAb derived from the parental mAb S309, a mAb directed against the spike protein of SARS-CoV-1 that potently cross-neutralizes SARS-CoV-2, the causative agent of COVID-19. The Fc domain of sotrovimab includes the 2 amino acid “LS” modification that extends antibody t1/2 and is also expected to enhance distribution to the respiratory mucosa. Sotrovimab received EUA for the treatment of mild-to-moderate COVID-19 in the US on 26 May 2021. At the time of this amendment, due to the high frequency of sub-variants against which sotrovimab has reduced in vitro neutralization, the FDA determined that sotrovimab is not currently authorized for use in any US region.

This is a Phase 1 healthy participant study with 3 Parts (Part A, Part B, and Part C). The study will evaluate both IM and IV routes of administrations at different doses and different IM sites of administration.

Part A and an optional Part B of this study are open-label and will evaluate the safety, tolerability, and relative bioavailability of the 62.5 mg/mL concentration and the new 100 mg/mL concentration of sotrovimab following IM injections at different sites.

Part C of this study is open-label and will characterize the safety and tolerability of sotrovimab administered intravenously in Cohort 1 and an optional Cohort 2.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Pharmacokinetics **Part A:** To estimate the relative bioavailability of 100 mg/mL IM sotrovimab at the dorsogluteal injection site relative to the 62.5 mg/mL formulation administered dorsogluteally through Day 29	Sotrovimab PK parameters: AUCD1-29 and Cmax
Safety **Part A:** • To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab and the 62.5 mg/mL formulation at the dorsogluteal injection site through Day 29 **Part C:** • To evaluate the safety and tolerability profile of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29	Incidence of AEs, SAEs, and AESI through Day 29
Secondary	
Pharmacokinetics **Part A:** • To estimate the relative bioavailability of 100 mg/mL IM sotrovimab at 2 alternative injection sites (anterolateral thigh and deltoid) relative to the 62.5 mg/mL formulation administered dorsogluteally through Day 29 **Part B:** • To estimate the relative bioavailability of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab at up to 2 injection sites relative to the 62.5 mg/mL formulation administered dorsogluteally through Day 29 **Part C:** • To characterize the PK of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29	Sotrovimab PK parameters: AUCD1-29 and Cmax
Pharmacokinetics **Part A:**	Sotrovimab PK parameter: AUCinf

Objectives	Endpoints
• To estimate the relative bioavailability of 100 mg/mL IM sotrovimab at 3 injection sites (dorsogluteal, anterolateral thigh, and deltoid) relative to the 62.5 mg/mL formulation administered dorsogluteally through Week 24 **Part B:** • To estimate the relative bioavailability of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab at up to 2 injection sites relative to the 62.5 mg/mL formulation administered dorsogluteally through Week 24	
Pharmacokinetics **Part A and Part B:** • To characterize the PK of 100 mg/mL and 62.5 mg/mL IM sotrovimab through Day 29 and Week 24 **Part C:** • To characterize the PK of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29 and Week 24	• Serum PK of sotrovimab
Safety **Part A:** • To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab administered at anterolateral thigh and deltoid injection sites and the 62.5 mg/mL formulation administered dorsogluteally through Day 29 • To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab administered at the dorsogluteal, anterolateral thigh, and deltoid injection sites and the 62.5 mg/mL formulation administered dorsogluteally through Week 35 **Part B:** • To evaluate the safety and tolerability profile of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab administered at up to 2 injection sites through Day 29 and Week 35 **Part C:** • To evaluate the safety and tolerability profile of IV sotrovimab in Cohort 1 and/or Cohort 2 through Week 35	**Part A and Part B:** • Incidence of AEs, SAEs, and AESI through Day 29/Week 35 **Part C:** • Incidence of AEs, SAEs, and AESI through Week 35

Overall Design:

This is a Phase 1, parallel group, randomized, single-dose study to evaluate the PK, safety, and tolerability of IM and IV sotrovimab, at different concentrations, doses, routes, and/or sites of administration, in male or female healthy participants aged 18 to 65 years.

The study consists of 3 parts (Part A, an optional Part B, and Part C).

Part A and Part B will be open-label and the enrollment will be sequential, starting with Part A. Part A and Part B participants will receive a single 500 mg dose of sotrovimab for IM injection.

Part C will be open-label, wherein participants in Cohort 1 will receive a single 3000 mg dose of IV sotrovimab infused over 60 minutes and participants in optional Cohort 2 will receive up to 3000 mg dose of IV sotrovimab infused over the time period to be specified in the pharmacy manual.

Brief Summary:

The purpose of this study is to evaluate PK, safety, and tolerability of sotrovimab administered by IM injection or IV infusion in healthy participants aged 18 to 65 years.

Study details include:

- Study Duration:

  The study duration is 35 weeks after dosing. Participants can be screened up to 28 days before dosing; therefore, the maximum duration a participant will be in the study is 39 weeks.

- Treatment Duration:
  - Part A and Part B: A single dose of 500 mg IM sotrovimab injection will be administered on Day 1.
  - Part C: A single infusion of 3000 mg IV sotrovimab in Cohort 1 and up to 3000 mg IV sotrovimab in optional Cohort 2 will be administered on Day 1.

- Visit Frequency:
  - In Part A, Part B, and Part C, on Day 1, participants will have a study site visit for study intervention administration. Additionally, participants in Part A and Part B will need to complete a PRO assessment at home on Day 1, and will also need to complete a PRO assessment at the site on Days 2, 3, 5, and 8.
  - In all Parts, participants will need to return to the study site on Days 2, 3, and 5 and at Weeks 2, 3, and 4 (Day 29). At Weeks 8, 12, 20, and 24, the participants will also need to return to the site or have a home visit.
  - In Part A, Part B, and Part C, at Week 35, the participants will have a phone call visit.

Number of Participants:

Part A:

Part A will consist of 4 treatment arms. Participants will be randomized in a 2:2:1:1 ratio to 4 treatment arms, as described under "Intervention Groups and Duration".

Approximately 190 participants will be enrolled assuming a 20% rate of non-evaluable participants to achieve approximately 150 evaluable participants across the 4 treatment arms.

Part B:

Part B is optional and will consist of either 1 or 2 treatment arms (N=32/arm), described under "Intervention Groups and Duration".

Approximately 32 participants will be enrolled per treatment arm assuming a 20% rate of non-evaluable participants to achieve approximately 25 evaluable participants within each treatment arm.

If 2 treatment arms are opened in parallel in Part B, then participants will be equally randomized to both treatment arms. However, if only 1 treatment arm is opened for Part B or 2 treatment arms are opened sequentially, then participants will not be randomized.

Part C:

Part C will consist of one cohort (Cohort 1: 3000 mg) with an additional optional cohort (Cohort 2: up to 3000 mg) to potentially explore further IV doses of sotrovimab and/or alternative infusion rates. This is further described under "Intervention Groups and Duration." Cohort 1 and optional Cohort 2 enrollment are sequential.

Approximately 200 evaluable participants (intend to target up to approximately 20 Japanese participants) will be enrolled to Cohort 1, and approximately 50 evaluable participants will be enrolled to Cohort 2 to supplement the Cohort 1 data.

Evaluable participants:

Part A and Part B:

Evaluable participants are defined as those who have PK concentration data to allow estimation of the primary endpoints (i.e., AUCD1-29 and Cmax).

Part C:

Evaluable participants are defined as those who have received study intervention.

Intervention Groups and Duration:

For all three parts of the study, screening assessment will be performed within 28 days prior to dosing, leading to a maximum study duration of 39 weeks.

Part A:

Participants will be randomized in a 2:2:1:1 ratio to the following 4 treatment arms:

- 500 mg IM of 62.5 mg/mL sotrovimab administered into the dorsogluteal muscles
- 500 mg IM of 100 mg/mL sotrovimab administered into the dorsogluteal muscles
- 500 mg IM of 100 mg/mL sotrovimab administered into the anterolateral thigh muscles
- 500 mg IM of 100 mg/mL sotrovimab administered into the deltoid muscles

Approximately 63 participants will be randomized to each of the 62.5 mg/mL and 100 mg/mL dorsogluteal arms, respectively, and approximately 32 participants will be randomized to each of the 100 mg/mL anterolateral thigh and deltoid arms, respectively.

Participants will be stratified by sex and 2 BMI strata (18 to ≤25 and >25 to 30 kg/m^2) to aim for a balance of treatment arms within each stratum in the study.

Part B:

Part B is optional and will consist of 1 or 2 treatment arms with 32 participants per treatment arm, to allow for assessment of 500 mg IM dose of 100 mg/mL and/or 62.5 mg/mL sotrovimab administered at the same and/or different injection volume/number of injections/sites of injections than those evaluated in Part A. Potential injection sites to be evaluated in Part B include deltoid, thigh, dorsogluteal, and/or ventrogluteal. Part B will start enrolling participants once Part A has completed enrollment.

Participants will be enrolled to target a similar representation of sex and BMI groups with those from Part A.

Part A and Part B:

For both Part A and Part B, injection volumes in the deltoid muscle will not exceed 2.5 mL/injection and injection volumes in thigh and gluteal muscles will not exceed 5 mL/injection. Follow-up will occur via site and home visits for 24 weeks, a phone call visit at Week 35, and PRO assessments through Day 8.

Part C:

Part C will assess a single 3000 mg dose of IV sotrovimab in Cohort 1 and up to 3000 mg dose of IV sotrovimab in an optional Cohort 2 in healthy participants.

The sotrovimab formulation used in this part will be the 100 mg/mL concentration, which will be diluted as described in the pharmacy manual prior to administration.

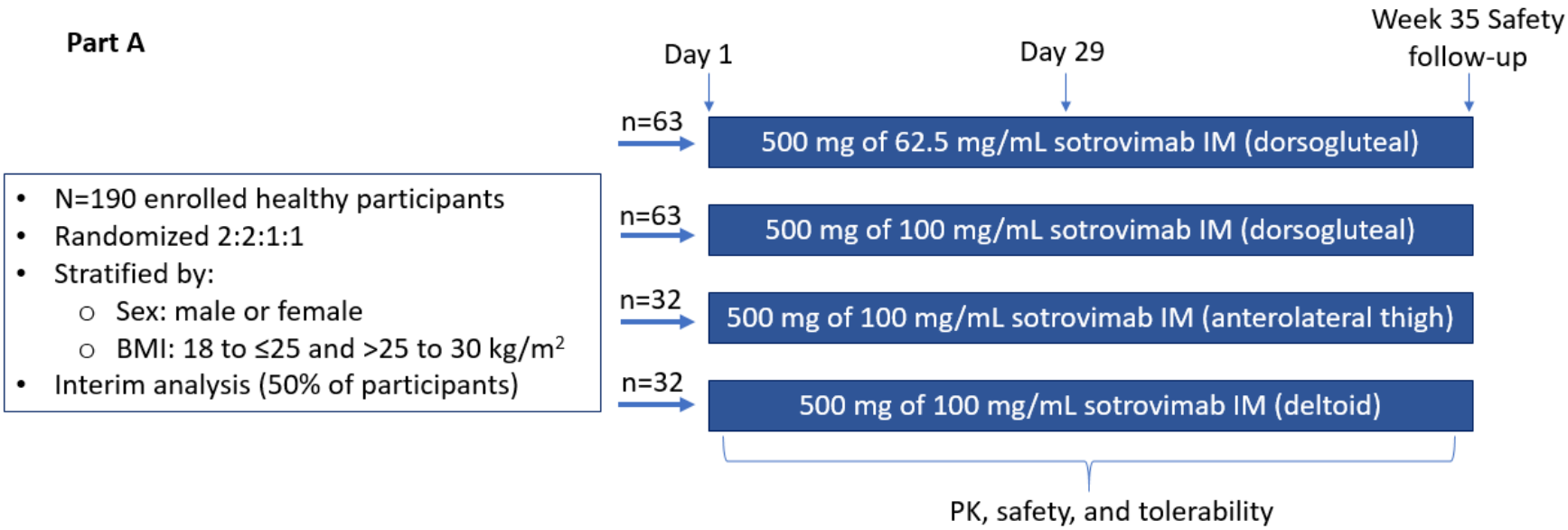
The enrollment of Part C participants will not be linked to Part A and Part B enrollment.

Data Monitoring/Other Committee:

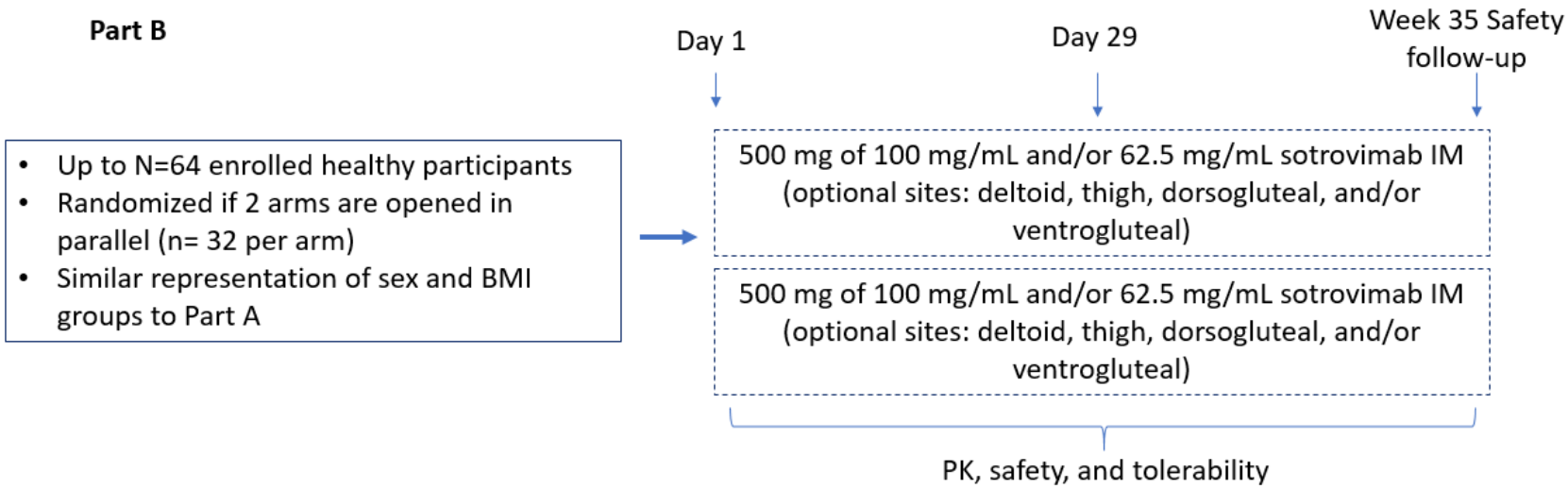
A JSRT will perform the following reviews during the study:

- Review of safety data at regular intervals as described in the JSRT charter.
- Review of data from a sentinel cohort for Part A and Part B will occur after all of the treatment arms within a study Part have approximately 5 participants who have completed at least Day 8. The JSRT will decide for each treatment arm whether to:
    - continue enrollment
    - stop enrollment
    - have the dose administered using a lower volume of injection by increasing the number of injections (e.g., 2 injections consisting of 2.5 mL instead of 1 injection consisting of 5 mL)
    - enroll an additional 5 participants per treatment arm before making a decision.
- Review of data from Part A to inform the decisions on whether to proceed with Part B and which treatment arms would be included in Part B.
- Review of data for Part C:
    - An in-stream safety lead-in data review will occur after approximately 30 participants in Cohort 1 have completed at least Day 8. JSRT will decide whether to continue with Cohort 1 and may request additional data before making a decision.
    - No dosing of further participants will take place until after the review is completed.

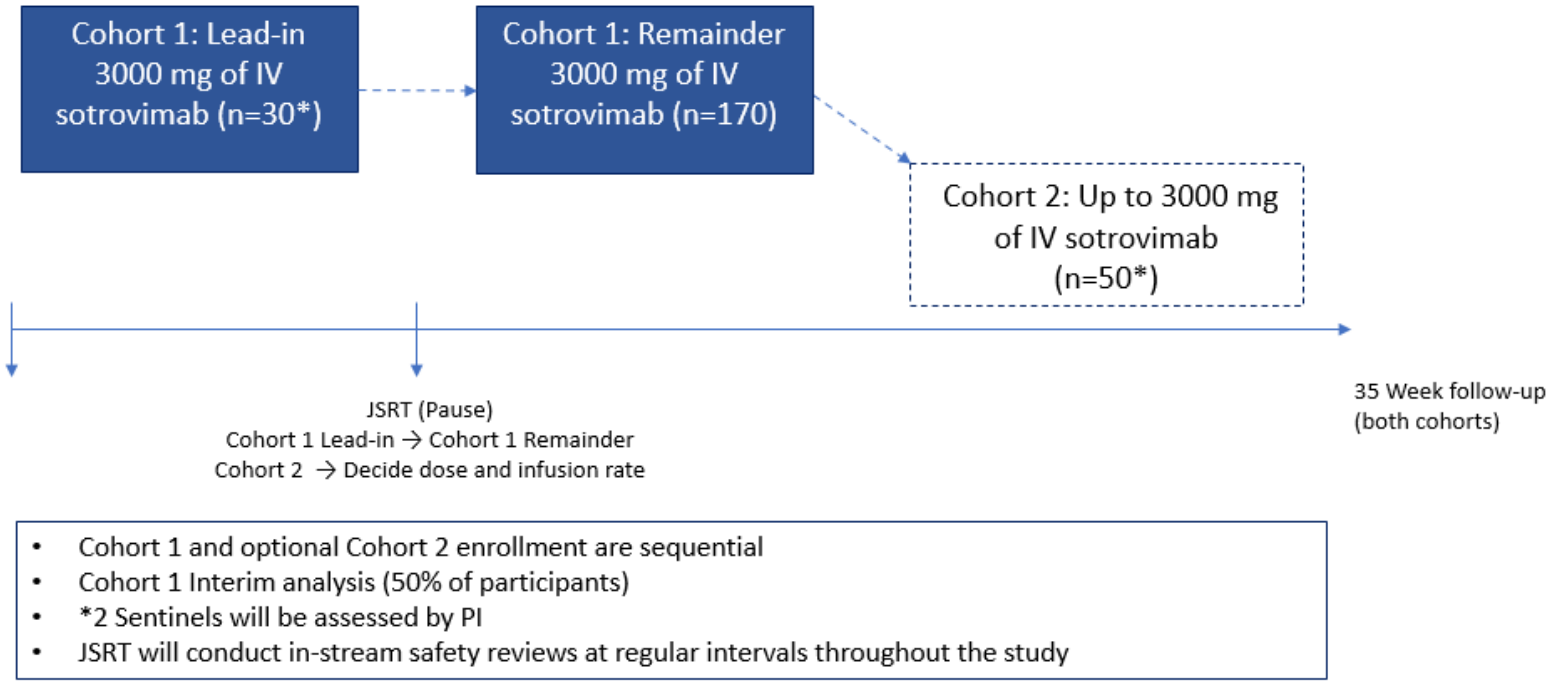
1.2. Schema


Part A
Day 1
Day 29
Week 35 Safety follow-up
N=190 enrolled healthy participants
Randomized 2:2:1:1
Stratified by:
Sex: male or female
BMI: 18 to ≤25 and >25 to 30 kg/m2
Interim analysis (50% of participants)
n=63
500 mg of 62.5 mg/mL sotrovimab IM (dorsogluteal)
n=63
500 mg of 100 mg/mL sotrovimab IM (dorsogluteal)
n=32
500 mg of 100 mg/mL sotrovimab IM (anterolateral thigh)
n=32
500 mg of 100 mg/mL sotrovimab IM (deltoid)
PK, safety, and tolerability

Part B


Day 1
Day 29
Week 35 Safety follow-up
• Up to N=64 enrolled healthy participants
• Randomized if 2 arms are opened in parallel (n= 32 per arm)
• Similar representation of sex and BMI groups to Part A
500 mg of 100 mg/mL and/or 62.5 mg/mL sotrovimab IM (optional sites: deltoid, thigh, dorsogluteal, and/or ventrogluteal)
500 mg of 100 mg/mL and/or 62.5 mg/mL sotrovimab IM (optional sites: deltoid, thigh, dorsogluteal, and/or ventrogluteal)
PK, safety, and tolerability

Part C



- Cohort 1 and optional Cohort 2 enrollment are sequential
- Cohort 1 Interim analysis (50% of participants)
- *2 Sentinels will be assessed by PI
- JSRT will conduct in-stream safety reviews at regular intervals throughout the study

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities: Part A and Part B

				W1				W2	W3	W4	W8	W12	W20	W24	W35	
	Study Visit Day ± Visit Window	**Screening[1] (up to Day -28)**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5±1d**	**Day 8±1d**	**Day 15±1d**	**Day 29±2d**	**Day 57±4d**	**Day 85±7d**	**Day 140±7d**	**Day 168±7d**	**Day 245±7d**	**Notes[16]**
	Site visit (S), home visit (H), or call (C)	S	S	S	S	S	S	S	S	S	S/H	S/H	S/H	S/H	C	NOTE: Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, 12-lead ECG, and blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. The actual time of assessment or procedure must be reported in the eCRF.
	Informed consent	X														1. All screening procedures must be completed within 28 days prior to dosing.
	Demographics	X														2. Provide details of any changes to medical history since Screening.
	Medical history (including medication/drug/alcohol/tobacco use, allergies, illnesses, and SARS-CoV-2 infection/therapy/vaccination)	X	X[2]													3. Including height and weight.
	Randomization			X												4. Record Day 1 vital signs within 1 hour prior to dosing, and immediately after injections. Vital signs will be monitored at approximately 15 minutes, 30 minutes, and 1 hour after dosing. Vital signs on other days should be performed once at any time of the day.
	Study intervention administration			X												
Assessments	Complete (C) or brief (B) physical examination	C[3]		B		B	B									
Assessments	Vital signs (BP, PR, RR, temperature, SpO_2)[4]	X		X[4]	X	X	X	X	X	X	X	X	X	X		
Assessments	Local injection site tolerability assessment			X[5]	X[5]	X[5]	X[5]	X[5]								5. Local injection site tolerability assessment on Day 1 at approximately 15 minutes, 30 minutes, and 1 hour post-dose and on Day 2, Day 3, Day 5, and Day 8. All ISRs need to be followed by the PI to resolution.
Assessments	12-lead ECG	X[6]														6. Triplicate 12-lead ECGs will be collected at Screening.
Assessments	PIN_TS3.0[7]			X	X	X	X	X								7. On Day 1, PIN_TS3.0 assessment will be performed before bedtime (at home). Assessments on Days 2, 3, 5, and 8 will be performed when participants arrive at the site.
Assessments	Pain-NRS[8]			X	X	X	X	X								
Sample collection	Safety laboratory assessments (hematology[10], clinical chemistry, coagulation)	X	X[9]		X		X	X		X	X	X		X		8. On Day 1, Pain-NRS will be assessed at 15 minutes, 30 minutes, and 1 hour after dosing (at site) and before bedtime (at home). Assessments on Days 2, 3, 5, and 8 will be performed when participants arrive at the site.
Sample collection	Urinalysis and urine albumin to creatinine ratio	X	X					X	X	X	X			X		
Sample collection	Urine drug/alcohol screening	X		X												9. Baseline laboratory assessments should be collected on Day -1.
Sample collection	HIV, Hepatitis B and C screening	X														
Sample collection	SARS-CoV-2 molecular test[11]	X	X													10. Hematology assessments will be performed only on Days -1, 2, 5, 8, and 29.
Sample collection	Pregnancy test[12]	X	X											X		
Sample collection	Blood sample for PK analysis[13]			X[13]	X	X	X	X	X	X	X	X	X	X		11. Screening and Day -1 tests must be >24 hours apart.
Sample collection	Blood sample for immunogenicity testing (ADA and drug-neutralizing antibody)			X[14]						X		X	X	X		12. Urine or serum pregnancy test, as per local guidelines. See Section 8.3.5.
Sample collection	CCI [redacted]															
	AE review			<========== X ==========>												13. Day 1 sample collection will occur pre-dose, and at 1, 2, 6, 8, 24 (Day 2), and 48 (Day 3) hours after the first injection. On other days, samples will be collected once at any time during the day.
	SAE review	X[15]	X[15]	<========== X ==========>												

AESI and concomitant medication review			<========== X ==========>	14. On Day 1, sample collection will occur pre-dose. 15. At Screening and on Day -1, only SAEs related to study participation or a GSK product will be reported. 16. If participant withdraws early from the study prior to Week 24, then the W24 visit assessments will be performed as the ED/EW visit. If the participant withdraws early from the study after Week 24, the W35 visit assessments will be performed as the EW visit.

Table 2 Schedule of Activities: Part C

	Study Visit Day ± Visit Window	Screening[1] (up to Day -28)	Day -1	W1 Day 1	W1 Day 2	W1 Day 3	W1 Day 5±1d	W2 Day 8±1d	W3 Day 15±1d	W4 Day 29±2d	W8 Day 57±4d	W12 Day 85±7d	W20 Day 140±7d	W24 Day 168±7d	W35 Day 245±7d	COVID-19 Test
	Site visit (S), home visit (H), or call (C)	S	S	S	S	S	S	S	S	S	S/H	S/H	S/H	S/H	C	S/C
	Informed consent	X														
	Demographics	X														
	Medical history (including medication/drug/alcohol/tobacco use, allergies, illnesses and SARS-CoV-2 infection/therapy/vaccination)	X	X[2]													
	Study intervention administration			X												
Assessments	Complete (C) or brief (B) physical examination	C[3]		B		B	B									
Assessments	COVID-19 signs/symptoms review			X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments	Vital signs (BP, PR, RR, temperature, SpO_2)[4]	X		X[4]	X	X	X	X	X	X	X	X	X	X		
Assessments	12-lead ECG	X[5]		X[5]	X[5]			X[5]								
Sample collection	Safety laboratory assessments (hematology[7], clinical chemistry, coagulation)	X	X[6]		X	X	X	X	X	X	X	X		X		
Sample collection	Urinalysis and urine albumin to creatinine ratio	X	X					X	X	X	X			X		
Sample collection	Urine drug/alcohol screening	X		X												
Sample collection	HIV, Hepatitis B and C screening	X														
Sample collection	SARS-CoV-2 molecular test[8]	X	X													X
Sample collection	Pregnancy test[9]	X	X											X		
Sample collection	Blood sample for PK analysis[10]			X[10]	X	X	X	X	X	X	X	X	X	X		
Sample collection	Blood sample for immunogenicity testing (ADA and drug-neutralizing antibody)			X[11]						X		X	X	X		
	AE review			<========== X ==========>												
	SAE review	X[12]	X[12]	<========== X ==========>												
	AESI and concomitant medication review			<========== X ==========>												

Notes[13]

NOTE: Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, 12-lead ECG, and blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. The actual time of assessment or procedure must be reported in the eCRF.

1. All screening procedures must be completed within 28 days prior to dosing.
2. Provide details of any changes to medical history since Screening.
3. Including height and weight.
4. Record Day 1 vital signs within 1 hour prior to IV Infusion, and immediately after IV infusions. Vital signs will be monitored at approximately 15 minutes, 30 minutes, 45 minutes, 1 hour, and 2 hours post dose. Participants will remain on site for 8 hours post-administration of study intervention for PK assessments. They will also have vitals measured prior to discharge. Vital signs on other days should be performed once at any time of the day.
5. Triplicate 12-lead ECGs will be collected at Screening. Single ECG will be performed on Day 1 (post dose) and Days 2 and 8 unless an abnormality is noted, in which case a triplicate ECG should be obtained.
6. Baseline laboratory assessments should be collected on Day -1.
7. Hematology assessments will be performed only on Days -1, 2, 5, 8, 15 and 29.
8. Screening and Day -1 tests must be >24 hours apart. [redacted]
9. Urine or serum pregnancy test, as per local guidelines. See Section 8.3.5.
10. On Day 1, PK sample collection will occur pre-dose, end of infusion, and at approximately 1, 2, 6, and 8 hours following end of infusion. On other days, PK samples will be collected once per visit.
11. On Day 1, sample collection will occur pre-dose.
12. At Screening and on Day -1, only SAEs related to study participation or a GSK product will be reported.
13. If participant withdraws early from the study prior to Week 24, then the W24 visit assessments will be performed as the ED/EW visit. If the participant withdraws early from the study after Week 24, the W35 visit assessments will be performed as the EW visit.

Abbreviations: Ab = antibody; ADA = anti-drug antibodies; AE = adverse event; AESI = adverse events of special interest; anti-N = anti-nucleocapsid; anti-S = anti-spike; BP = blood pressure; COVID-19 = Coronavirus disease 2019; d = day; GSK = GlaxoSmithKline; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EW = early withdrawal; HIV = human immunodeficiency virus; PI = principal investigator; PK = pharmacokinetic; PR = pulse rate; RR = respiratory rate; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SpO_2 = oxygen saturation; W = week.

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor/designee and site study files but will not constitute a protocol amendment.
- The CA and EC will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 1, parallel group, randomized, single-dose study to evaluate the PK, safety, and tolerability of IM and IV sotrovimab, at different concentrations, doses, routes, and/or sites of administration, in male or female healthy participants aged 18 to 65 years.

Preventing infection and reducing the risk of progression of COVID-19 remains an urgent public health priority. While currently available vaccines have been shown to be highly efficacious, the elderly population and those with comorbidities remain at higher risk of hospitalization following COVID-19 infection than the general population. Many patients who are at high risk of hospitalization with COVID-19 require extensive in-hospital care, including ICU and mechanical ventilation, which heightens the resource burden on hospitals, particularly during infection peak periods. There remains an unmet need for effective treatments to prevent infection and prevent the progression from mild to severe disease and treat severe disease.

As the COVID-19 pandemic continues to evolve with the rapid evolution of VOI/VOCs, healthcare professionals treating COVID-19 infections will need to identify the best treatment for their patient based on the circulating variants and underlying comorbidities.

In addition to the current 62.5 mg/mL concentration, a 100 mg/mL ready-to-fill bulk drug substance, leveraging the same formulation, is being pursued in an effort to lower the injection volume when injected intramuscularly. This will allow additional injection sites to be used. The 100 mg/mL concentration is also being studied as an IV infusion. Both release testing and extended characterization results for the Gen2, 100 mg/mL samples showed a high degree of comparability to results from the Gen2 62.5 mg/mL batches, with the exception of attributes expected to be impacted by the change in product concentration and change in vial configuration.

Considering the infrastructural and infection control-related concerns associated with IV mAbs for SARS-CoV-2, there remains a critical unmet medical need for treatments with a convenient route of administration [Sitlani, 2021; Snowbeck, 2021]. A mAb administered via IM injection could increase access in the outpatient setting and among certain groups who may be at high risk for severe disease. Administration via IM dosing could also reduce the drug delivery-related burden on the healthcare system [Lin, 2021; Ordal, 2021; Sakata T, 2021; Traynor, 2021], substantially increasing the availability of efficacious early treatment for patients with COVID-19 at high risk for disease progression.

Sotrovimab has been studied in a Phase 3 placebo-controlled study evaluating the efficacy of sotrovimab in preventing progression of COVID-19 in high-risk participants with mild/moderate COVID-19 (VIR-7831-5001; COMET-ICE). On 10 March 2021, the Independent Data Monitoring Committee for COMET-ICE recommended that the study be stopped for enrollment due to evidence of clinical efficacy. This was based on an interim analysis of data from 583 participants which demonstrated an 85% (p=0.002)

reduction in hospitalization or death in participants receiving sotrovimab compared to placebo. Sotrovimab was well-tolerated with no safety signals detected [Vir, 2021].

The COMET-TAIL study was then designed to assess the efficacy, safety, and tolerability of IM sotrovimab versus IV sotrovimab when given to high-risk participants for the treatment of mild/moderate COVID-19. This study evaluated the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab in preventing progression of COVID-19 by utilizing a NI design. Enrollment was completed on 19 August 2021 and the Day 29 analysis indicated the following: in the IM administration (500 mg) arm of the study, there was a 2.7% rate of progression to hospitalization for more than 24 hours or death through Day 29 of the study, compared to 1.3% in the IV administration arm (also 500 mg). The adjusted difference between the IM and IV arms of the study was 1.11% with a 95% CI of -1.24% to 3.45%. The upper bound of the 95% CI was within the predetermined 3.5% NI margin set for the study's primary endpoint in consultation with the US FDA. Sotrovimab 500 mg IM injection was found to be well-tolerated and non-inferior to IV administration [Shapiro, 2022].

Since then, several factors have contributed to the need for evaluation of different doses of sotrovimab. First, the emergence of the Omicron variant and its sub-lineages have caused the landscape to evolve substantially as described in the COVID-19 treatment guidelines from the NIH [NIH, 2022].

This COSMIC study consists of 3 parts (Part A, an optional Part B, and Part C). The aim of Part A of this study is to provide the safety, tolerability, and relative bioavailability data to support the transition from the current concentration of 62.5 mg/mL to the higher concentration of 100 mg/mL of 500 mg IM sotrovimab following dorsogluteal injection and to explore 2 additional IM injection sites: anterolateral thigh and deltoid.

Part B of this study is optional and will allow an assessment of 500 mg IM dose of 100 mg/mL and/or 62.5 mg/mL sotrovimab administered at the same and/or different injection sites or volumes than those evaluated in Part A. Potential injection sites to be evaluated in Part B include deltoid, thigh, dorsogluteal, and/or ventrogluteal.

Part C of this study is an open-label, single IV infusion part to characterize the safety and tolerability of 3000 mg sotrovimab in Cohort 1 and up to 3000 mg sotrovimab in an optional Cohort 2. Cohort 2 will be opened to potentially assess a different infusion rate and/or dose than Cohort 1. A decision on whether to proceed with Cohort 2 including the selection of dose and infusion rate will be made by the JSRT and the clinical team based on the review of safety lead-in data from Cohort 1. This will provide safety and tolerability data to support the intended clinical doses to be evaluated in COVID-19 treatment and prophylactic indications.

2.2. Background

In December 2019, SARS-CoV-2, a novel betacoronavirus, was first reported to cause severe pneumonia in Wuhan, China and subsequently had a rapid spread around the world. As of 11 August 2022, 587,497,872cases of COVID-19 have been reported globally, including 6,427,420 associated deaths [Johns Hopkins University and Medicine,

2022]. As of 11 August 2022, around 92,296,142 cases have been reported with over 1,030, 010 associated deaths in the US [CDC, 2022].

Sotrovimab is being developed for treatment of COVID-19. Sotrovimab is a human IgG1κ mAb derived from the parental mAb S309, a mAb directed against the spike protein of SARS-CoV-1 that potently cross-neutralizes SARS-CoV-2, the causative agent of COVID-19 [Pinto, 2020]. Sotrovimab received EUA and temporary market authorization based on the results from VIR-7831-5001 (214367, also known as COMET-ICE [NCT04545060]). COMET-ICE is a seamless FIH/Phase II/III study assessing the safety and efficacy of a single 500 mg IV dose of sotrovimab for the early treatment of COVID-19 in non-hospitalized participants at high risk for progression and subsequent hospitalization.

Sotrovimab retains neutralization activity in vitro against almost all of the current VOCs/VOIs of the SARS-CoV-2 virus as defined by the World Health Organization, including, but not limited to, B.1.1.7 (Alpha, UK origin), B.1.351 (Beta, South Africa origin), P.1 (Gamma, Brazil origin), B.1.427/B.1.429 (Epsilon, California origin) B.1.526 (Iota, New York origin), B.1.617.1 (Kappa, India origin), B.1.617.2 (Delta, India origin), AY.1 (Delta Plus, India origin), AY.2 (Delta Plus, India origin), C.37 (Lambda, Peru origin), B.1.621 (Mu, Colombia origin), and B.1.1.529 (Omicron, South Africa origin) [Cathcart, 2022] variant spike proteins with fold-changes in EC50 values of less than 5-fold as compared to wild-type spike. In vitro neutralization experiments indicate that sotrovimab neutralizes authentic Omicron BA.2 virus with a 15.7-fold change in EC50 value relative to wild-type [Cathcart, 2022]. Sotrovimab neutralized authentic Omicron BA.2 virus with a geometric mean EC90 value of 9476.3 ng/mL (range: 6796.8 to 14760.0 ng/mL; 35.1-fold change in EC90 value relative to wild-type) (PC-7831-0155). Sotrovimab neutralized authentic Omicron BA.4 and Omicron BA.5 virus with an EC50 value of 2650.7 ng/mL (48.4-fold change) and 1001.2 (21.6-fold change), respectively (PC-22-0117).

2.2.1. Clinical Experience with Sotrovimab

As of 18 August 2021, a total of 1843 participants have received sotrovimab (500 mg dose) administered IV or IM in the Vir sponsored clinical studies.

Sotrovimab received an EUA and temporary market authorization based on the results from the VIR-7831-5001 study (GSK Study 214367, also known as COMET-ICE). COMET-ICE is a seamless FIH/Phase II/III study assessing the safety and efficacy of a single 500 mg IV dose of sotrovimab for the early treatment of COVID-19 in non-hospitalized participants at high risk for progression and subsequent hospitalization.

Other ongoing Vir-sponsored study includes COMET-TAIL (NCT04913675), and completed studies include COMET-PEAK (VIR-7831-5006/GSK Study 216912; NCT04779879) and a pharmacokinetic (PK) study with Japanese participants (VIR-7831-5009/GSK Study 217653; NCT04988152). A summary of SAE and other safety data are included for these studies in the IB update, version 3. GSK has been supporting Vir in the conduct of the Vir-sponsored clinical studies.

GSK is sponsoring an ongoing pediatric clinical study (COMET-PACE [GSK Study 215226/VIR-7831-5005]) of sotrovimab in participants aged birth to <18 years.

In addition, Vir/GSK supported clinical studies (ACTIV-3-TICO [VIR-7831-5004, GSK Study 215149], BLAZE-4 [VIR-7831-5007, 217079], and Study 217940 [OPTIMISE-C19]) are evaluating sotrovimab as a single agent or in combination. Details of these studies are included in the IB update, version 3.

Sotrovimab at 1000 mg IV is also being evaluated in the UK-based RECOVERY platform study (NCT04381936). In this study, hospitalized participants with confirmed COVID-19 are randomized to receive different candidate therapies. The RECOVERY Trial Independent Data Monitoring Committee's 10 June 2022 review of safety and efficacy data, inclusive of 1070 participants that received 1000 mg IV sotrovimab, suggested no reason to modify the protocol [DMC Report, 2022].

Sotrovimab at 2000 mg IV is also being evaluated in the ongoing COMET-TAIL safety sub-study (VIR-7831-5008/GSK Study 217114; expected n=81) for early treatment and PROTECT-V study (Investigator Sponsored Study; GSK Study 218216; expected n=1760) for prophylaxis.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sotrovimab may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Sotrovimab		
Hypersensitivity reactions (HSRs) reported any time post dose	While sotrovimab is a human immunoglobulin G1 (IgG1) mAb, hypersensitivity is a potential general risk associated with the mAb class of therapeutics. Patients who are treated with monoclonal antibodies are at potential risk for developing HSR. This risk may be higher for higher doses or faster infusion rates. In Part C Cohort 1, 3000 mg of the study intervention will be administered over 60 minutes. It is the first time that this particular dose and infusion rate of sotrovimab have been used (refer to IB for further details of sotrovimab dose and infusion time previously used). There was no evidence of systemic infusion reactions in toxicology studies conducted with sotrovimab in monkeys. In COMET-ICE, all HSRs were non-serious, of Grade 1 (mild) or Grade 2 (moderate) severity and reported in 2% of participants who received sotrovimab and in <1% who received placebo (9 participants treated with sotrovimab; 5 participants treated with placebo). None of the reactions in either treatment arm led to pausing or discontinuation of the infusions. All events across both treatment groups were reported as resolved or resolving at the time of DCO. No anaphylaxis events were reported in the COMET-ICE study in participants with mild to moderate COVID-19 not requiring hospitalization at study entry. A potentially life-threatening allergic reaction (anaphylaxis) was observed in 1 adult participant who received sotrovimab in the study of individuals	• Participants will be excluded if they have a history of hypersensitivity to any of the constituents present in the investigational product. • Participants will be monitored for 1 hour in Part A and Part B. • Participants will remain on site for 8 hours post-administration of study intervention for PK assessments. They will also have vitals measured prior to discharge (see SoA in Section 1.3). • Investigational product will be administered in the clinic with staff trained in emergency care and resuscitation procedures and emergency care kit on hand during the study intervention administration and post-therapy observation periods. • In Part C, initial dosing in Cohort 1 and Cohort 2 will be staggered so that the first 2 participants will be considered sentinels and will be dosed at the same clinical trial site. After at least 24 hours (post dose), and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants will be dosed as non-sentinel participants.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	hospitalized with COVID-19 (the ACTIV-3-TICO study). Spontaneous post marketing cases of anaphylaxis have been reported. As of 16 March 2022, no anaphylaxis or serious HSRs were reported in any of the 500 mg IV, 500 mg IM, or 250 mg IM sotrovimab arms in COMET-TAIL study. The RECOVERY trial DMC letter dated 10 June 2022 noted that recruitment is ongoing and as of 07 June 2022, 1070 participants had been randomized 1:1 (sotrovimab: standard of care). This trial DMC letter (dated 10 June 2022) also confirmed that review of safety data on 1070 patients (1:1 sotrovimab: standard of care) was completed and that the trial may continue with no changes in conduct [DMC Report, 2022]. The RECOVERY team has confirmed that there have been only 2 related SAEs reported. The first was a case of suspected anaphylaxis treated with adrenaline. The participant apparently improved within 2 hours without further complication and was discharged 5 days later. The second was a rash shortly after finishing the infusion considered to be an HSR. The participant was discharged 2 days later.	• Approximately 30 participants will be enrolled in a safety lead-in in Part C Cohort 1, and relevant safety data through Day 8 will be reviewed by the JSRT. • The JSRT will review the safety data of this study at regular intervals. • In Part C Cohort 2, the dose and infusion rate of the study intervention will be decided based on a safety review of Cohort 1. • For details on discontinuation of study intervention and temporary discontinuation, refer to Section 7.1 and Section 7.1.2. • General guidance on management of HSRs is provided in Section 10.6. • Refer to Section 8.4.7 for follow up regarding AESI.
Infusion-Related Reactions (IRRs) within 24 hours post dose (Part C)	IRRs are a potential general risk for biologic therapies with IV administration. This risk may be higher for higher doses or shorter infusion times. However, sotrovimab and other COVID-19 mAbs have been generally well-tolerated. There was no evidence of infusion reactions in toxicology studies conducted with sotrovimab in monkeys. In the COMET-ICE study, in participants with mild/moderate COVID-19 with high risk of progression, IRRs that occurred within 24 hours post infusion (pyrexia, chills, dizziness, dyspnea, pruritus, rash, and IRR) were reported in 7 (1%) of participants in the sotrovimab arm and 6 (1%) of participants in the placebo arm. All IRRs were non-serious, and Grade 1 or 2 severity and none led to treatment interruption or discontinuation. In the sotrovimab arm, all of	• Participants will remain on site for 8 hours post-administration of study intervention for PK assessments. They will also have vitals measured prior to discharge (see SoA in Section 1.3). • In Part C, initial dosing in Cohort 1 and Cohort 2 will be staggered so that the first 2 participants will be considered sentinels and will be dosed at the same clinical trial site. After at least 24 hours (post dose), and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	the cases of IRRs were considered resolved and in the placebo arm 1 participant had an event considered not resolved at the time of EoS analysis (Week 24).	participants will be dosed as non-sentinel participants. • Approximately 30 participants will be enrolled in a safety lead-in in Part C Cohort 1, and relevant safety data through Day 8 will be reviewed by the JSRT. • Infusion time can be extended at the discretion of the Investigator or Sponsor based on infusion-related symptoms or other safety findings. • If a participant experiences a Grade 2 IRR, investigators will be instructed to pause the infusion. The infusion may subsequently resume at a slower pace of infusion, at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids). See Section 7.1.2. • Investigators are instructed to discontinue IV infusions for participants who develop Grade 3 or 4 infusion reactions using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) Adverse Event grading. See Section 10.3.3. • IV infusion will be administered in the clinic with staff trained in emergency care and resuscitation procedures and emergency care kit on hand during the infusion and post therapy observation periods. • Refer to Section 8.4.3 for follow up regarding AESI.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Injection Site Reaction (ISR) (Part A and Part B)	Sotrovimab will be administered via IM injection, which has a potential risk of local ISRs. In a single dose IM local tolerance study in mini pigs at a dose of 250 mg (4 mL, 62.5 mg/L), no ISRs were observed. The IM route of administration is being evaluated in the COMET-PEAK study. Injection site reactions (dorsogluteal) were reported in 10 out of 82 participants, who were included in the safety population for the IM dorsogluteal injection in COMET-PEAK Part B and showed an acceptable tolerability profile for IM [GlaxoSmithKline, 2021]. One ISR occurred immediately post-dose, and the rest occurred within the first hour post-dose. All of the ISRs were Grade 1.	• ISRs will be monitored very closely for 1 hour after injection and on Day 2, Day 3, Day 5, and Day 8 for all participants. Monitoring will also be performed for systemic symptoms post-dosing (e.g., fever, chills, malaise). • The JSRT will review safety data of this study at regular intervals as described in Section 10.1.5.1.
Immunogenicity	While sotrovimab is a human IgG, the development of ADA that have the potential to impact safety and/or efficacy are a potential general risk associated with the mAb class of therapeutics. Through Day 29 in the COMET-ICE study, the incidence of treatment-emergent anti-sotrovimab antibody responses has remained low with relatively low titers, with no detectable impact on safety or efficacy.	• This study includes collection of samples for assessment of ADA and potential impact on PK/PD and safety. ADA samples will be collected for a period of 24 weeks.
ADE due to sub-neutralizing /levels of sotrovimab enhancing fusion or leading to FcγR mediated increased viral uptake and replication with virus production; ADE due to enhanced disease pathology from viral antigen-antibody related immune complex deposition or complement activation and	This is a concern related to the potential for participants who are infected with COVID-19 after administration of study intervention with sub-neutralizing mAb levels to experience a higher incidence of infection and/or more severe disease compared to participants with no circulating mAb and/or established protective immunity to SARS-CoV-2. ADE associated with Dengue virus 1-4 serotype infections is one of the most widely cited examples in which reinfection with a different serotype can, in a minority of patients, run a more severe course in the setting of limited antibodies generated by prior infection. The potential for enhanced disease in this setting is due to increased uptake of virus by FcγR-expressing cells, such as macrophages, and increased viral	This study will include participant follow-up for a period of 35 weeks in all Parts to assess for the potential of enhanced disease in the context of waning sotrovimab levels. Periodic review of clinical signs and symptoms of COVID-19, clinical chemistry, AEs, end-organ disease and histopathological diagnoses will be performed by the JSRT to identify potential cases of immune complex disease. Assessments for unusually severe disease in mAb-treated participants will be performed by the JSRT.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
immune cell recruitment in target organs	replication in these cells. Recent data shows that SARS-CoV-2 does not replicate efficiently in macrophages [Hui, 2020], suggesting minimal to no risk of ADE via this mechanism. There is the possibility that a large amount of antibody that binds, but does not neutralize virus in the presence of a high viral load could result in immune complex deposition and complement activation in tissue sites of high viral replication, such as the lungs, vascular endothelia, renal or cardiovascular tissue [Hamming, 2004], leading to tissue damage/immune complex disease. This is hypothesized to have contributed to inflammation and airway obstruction observed in the small airways of infants who received a formalin-inactivated respiratory syncytial virus vaccine [Polack, 2002] and in a few cases of fatal H1N1 influenza infection [Wu , 2010]. The potential for enhanced disease in this setting may be due to low affinity or cross-reactive antibodies with poor or no neutralizing activity. Triggering of cytokine release by antibody-virus-FcγR interactions although usually highly beneficial due to their direct antiviral effects and immune cell recruitment to control viral spread in tissues, also has the potential to enhance pathologic changes initiated by the viral infection. Observational data from 20,000 COVID-19 patients treated with convalescent plasma, although not placebo controlled, is suggestive that even polyclonal mixtures of neutralizing and non-neutralizing antibodies can be safely administered [Joyner, 2020]. Sotrovimab shows potent binding in vitro as well as neutralization of pseudovirus and live virus thus this risk is deemed to be low. In clinical studies to date there is no evidence ADE associated with sotrovimab.	Infection will be assessed as new AEs/SAEs related to COVID-19 infection during follow-up period.

2.3.2. Benefit Assessment

There is an unmet need for treatments for COVID-19 both in an outpatient and inpatient setting. Participation in this study will provide valuable scientific knowledge about sotrovimab administered with different doses, routes, and concentrations. Sotrovimab is being developed for the treatment of COVD-19.

Part A and Part B of this study will evaluate the relative bioavailability, safety, and tolerability of the higher concentration IM sotrovimab at different sites of injection.

Data from Part C of the study may support dosing options for therapeutics and effective preventive measures for COVID-19 against emerging variants. This may include higher doses in hospitalized and non-hospitalized patients or repeat dosing in prophylaxis especially for vulnerable patients who do not respond optimally to vaccines or appropriate people who cannot tolerate COVID-19 vaccinations. In addition, given the pressure on healthcare resources during the pandemic and the need to find treatments that ease the burden on healthcare facilities, data from the study may support a range of infusion times to ensure continued access in an inpatient and outpatient setting.

No studies to assess direct benefit to healthy volunteers (e.g., as a prophylaxis) have been completed, although a pre-exposure prophylaxis study is underway and participants may benefit from an unknown duration of protection from COVID-19 disease (PROTECT-V GSK Study 218216). Therefore, no direct benefit for healthy participants in this study is currently known.

Sotrovimab has been demonstrated to be a highly potent human IgG1 neutralizing SARSCoV-2 antibody with additional antibody effector functions that has been well-tolerated to date. The nonclinical pharmacology, PK, toxicology, and clinical results to date support the evaluation of sotrovimab in healthy volunteers.

Mitigation strategies, including physical examinations and laboratory evaluations as outlined in the SoA (Section 1.3) are included to limit the risk to participants.

2.3.3. Overall Benefit: Risk Conclusion

The overall benefit-risk assessment considers the potential benefit of treatment for COVID-19 with IM and IV administration of sotrovimab.

Sotrovimab has the potential to be an effective therapeutic in mild to moderately ill participants with COVID-19. This benefit has been demonstrated among participants with mild to moderate COVID-19 at high risk of disease progression [Vir, 2021]. The data from this Phase 1 study may support future development of optionality in terms of IV doses and IM route of administration.

Human-derived mAbs with similar Fc modifications as sotrovimab have a well-established safety profile [Gaudinski, 2018].

To date, sotrovimab is well-tolerated in clinical trials with no safety concerns that would preclude single-dose evaluation in healthy volunteers.

There may be little or no direct benefit to healthy volunteers participating in the study beyond the knowledge that they may have contributed to the development of a medicine that may be used in the COVID-19 pandemic. A potential for benefit from prophylaxis from infection or progression to disease in those who acquire COVID-19 during the study may also exist, though this is as yet unproven and unquantified and may be negligible in a healthy volunteer population. The potential risks associated with sotrovimab can be appropriately mitigated by the proposed inclusion and exclusion criteria and safety monitoring procedures. As such, the risk to potential participants is considered low. The overall benefit-risk assessment of this study is considered favorable.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Pharmacokinetics **Part A:** To estimate the relative bioavailability of 100 mg/mL IM sotrovimab at the dorsogluteal injection site relative to the 62.5 mg/mL formulation administered dorsogluteally through Day 29	Sotrovimab PK parameters: AUCD1-29 and Cmax
Safety **Part A:** To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab and the 62.5 mg/mL formulation at the dorsogluteal injection site through Day 29 **Part C:** • To evaluate the safety and tolerability profile of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29	Incidence of all AEs, SAEs, and AESI through Day 29
Secondary	
Pharmacokinetics **Part A:** • To estimate the relative bioavailability of 100 mg/mL IM sotrovimab at 2 alternative injection sites (anterolateral thigh and deltoid) relative to the 62.5 mg/mL formulation administered dorsogluteally through Day 29 **Part B:** • To estimate the relative bioavailability of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab at up to 2 injection sites	Sotrovimab PK parameters: AUCD1-29 and Cmax

Objectives	Endpoints
relative to the 62.5 mg/mL formulation administered dorsogluteally through Day 29 **Part C:** • To characterize the PK of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29	
Pharmacokinetics **Part A:** • To estimate the relative bioavailability of 100 mg/mL IM sotrovimab at 3 injection sites (dorsogluteal, anterolateral thigh, and deltoid) relative to the 62.5 mg/mL formulation administered dorsogluteally through Week 24 **Part B:** • To estimate the relative bioavailability of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab at up to 2 injection sites relative to the 62.5 mg/mL formulation administered dorsogluteally through Week 24	Sotrovimab PK parameter: AUCinf
Pharmacokinetics **Part A and Part B:** • To characterize the PK of 100 mg/mL and 62.5 mg/mL IM sotrovimab through Day 29 and Week 24 **Part C:** • To characterize the PK of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29 and Week 24	• Serum PK of sotrovimab
Safety **Part A:** • To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab administered at anterolateral thigh and	**Part A and Part B:** • Incidence of AEs, SAEs, and AESI through Day 29/Week 35

Objectives	Endpoints
deltoid injection sites and the 62.5 mg/mL formulation administered dorsogluteally through Day 29 • To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab administered at the dorsogluteal, anterolateral thigh, and deltoid injection sites and the 62.5 mg/mL formulation administered dorsogluteally through Week 35 **Part B:** • To evaluate the safety and tolerability profile of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab administered at up to 2 injection sites through Day 29 and Week 35 **Part C:** • To evaluate the safety and tolerability profile of IV sotrovimab in Cohort 1 and/or Cohort 2 through Week 35	**Part C:** • Incidence of AEs, SAEs, and AESI through Week 35
Other Safety	
Part A and Part B: • To evaluate the safety and tolerability of sotrovimab following IM administration through Day 29 and Week 35 **Part C:** • To evaluate the safety and tolerability of IV sotrovimab in Cohort 1 and/or Cohort 2 through Day 29 and Week 35	• Incidence of clinically significant changes in vital signs and laboratory abnormalities change from baseline through Day 29 and Week 35
Exploratory	
PRO (Part A and Part B) • Evaluate the pain, ISR, and acceptability of both the 62.5 mg/mL and 100 mg/mL formulations of sotrovimab administered intramuscularly	• Totally acceptable or very acceptable pain and totally acceptable or very acceptable local reaction acceptability score on PIN_TS3.0 at Days 1, 2, 3, 5, and 8 • Pain intensity on pain-NRS at 15 minutes, 30 minutes and 1 hour after dosing and before bedtime on Day 1, and Days 2, 3, 5, and 8

Objectives	Endpoints
	• Scores of PIN_TS3.0 domains (bothersomeness of ISRs, impact on sleep, impact on movement), and scores of four individual items (anxiety before injection, bothersomeness during injection, satisfaction with the injection system, and willingness to receive as a treatment) on Days 1, 2, 3, 5, and 8

CCI [redacted]

Co-primary Estimands (Part A)

The primary clinical question of interest is: what is the relative bioavailability and safety profile of 100 mg/mL IM sotrovimab administered at the dorsogluteal injection site relative to the 62.5 mg/mL IM formulation administered dorsogluteally in participants through Day 29?

The PK primary estimand is described by the following attributes:

- Population: Male or female healthy participants aged 18 to 65 years who would be able to complete the IM dose.
- Endpoints: Sotrovimab serum PK parameters: AUCD1-29 and Cmax.
- Treatments: 100 mg/mL IM sotrovimab vs 62.5 mg/mL IM sotrovimab (dorsogluteal injections).
- Strategy for intercurrent event: The intercurrent event of interest is participants receiving an incomplete IM dose. The strategy for handling this intercurrent event will be a Principal Stratum Strategy, where we are only interested in the strata of participants who would be able to receive a complete IM dose. Exclusion of participants who did not receive a complete IM dose will not introduce bias as the reasons for dose interruption are not related to their PK.
- Population-level summary: The point estimate for the ratio of the geometric means of 100 mg/mL treatment group compared to the 62.5 mg/mL treatment group and the related 90% CI will be calculated.

The Safety primary estimand is described by the following attributes:

- Population: Male or female healthy participants aged 18 to 65 years.
- Endpoints: Incidence of all AEs, SAEs, and AESI through Day 29 (i.e., all events on the database at the time of DCO).
- Treatments: 100 mg/mL IM sotrovimab and 62.5 mg/mL IM sotrovimab (dorsogluteal injections).
- Strategy for intercurrent event: The intercurrent event of interest is participants receiving an incomplete IM dose. The strategy for handling this intercurrent event will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included.
- Population-level summary: Frequency and percentage of participants.

Primary Estimand (Part C)

The primary clinical question of interest is: what is the safety and tolerability of IV infusion of sotrovimab at 3000 mg dose in Cohort 1 and also not exceeding 3000 mg dose in an optional Cohort 2?

The Safety primary estimand is described by the following attributes:

- Population: Male or female healthy participants aged 18 to 65 years.
- Endpoints: Incidence of all AEs, SAEs, and AESI through Day 29 (i.e., all events on the database at the time of DCO).
- Treatments: Single IV infusion of sotrovimab at 3000 mg dose in Cohort 1 and single IV infusion of sotrovimab at up to 3000 mg dose in an optional Cohort 2.
- Strategy for intercurrent event: The intercurrent event of interest is participants receiving an incomplete IV dose. The strategy for handling this intercurrent event

will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included.

- Population-level summary: Frequency and percentage of participants.

Rationale for Estimands:

Two different strategies are proposed for the same intercurrent event of participants receiving an incomplete IM/IV dose, as interest lies in:

- the PK of treatment effect in participants who received complete dose, and
- safety of treatment effect for any level of exposure to study intervention.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, parallel group, randomized, open-label, single-dose study to evaluate the PK, safety, and tolerability of IM and IV at different concentrations, doses, routes, and/or sites of administration, in male or female healthy participants aged 18 to 65 years.

The study consists of 3 parts (Part A, an optional Part B, and Part C).

The aim of Part A of this study is to evaluate the safety, tolerability, and relative bioavailability of the 62.5 mg/mL concentration and the new 100 mg/mL concentration of sotrovimab following dorsogluteal injection, as well as the relative bioavailability of the 100 mg/mL concentration at 2 additional IM injection sites, anterolateral thigh, and deltoid.

The aim of Part B of this study, if conducted, is to evaluate the relative bioavailability of 100 mg/mL and/or 62.5 mg/mL IM sotrovimab at up to two injection sites (deltoid, thigh, dorsogluteal, and/or ventrogluteal) relative to the 62.5 mg/mL dorsogluteal arm that is enrolled in Part A, as well as characterize the PK and evaluate the safety of 100 mg/mL sotrovimab at up to two injection sites.

Enrollment will be sequential for Parts A and B, starting with Part A. An IA will be performed once half of the participants in Part A complete at least Day 8. A decision on whether to proceed with Part B will be made by the JSRT and the clinical team after the IA. If the decision is made to proceed with Part B, then Part B of this study will include 1 or 2 treatment arms that would allow for the evaluation of additional injection volumes/number of injections/sites of injections than those evaluated in Part A. The decision about which treatment arms to include in Part B will be informed by tolerability data during part A and clinical considerations. Part B will start enrolling participants once Part A has completed enrollment.

The aim of Part C of this study is to characterize the safety and tolerability of single IV infusion of 3000 mg sotrovimab in Cohort 1 and up to 3000 mg sotrovimab in an optional Cohort 2. Cohort 2 will be opened to potentially assess a different infusion rate and/or dose than Cohort 1. The sotrovimab formulation used in this part will be the 100 mg/mL concentration, which will be diluted as described in the pharmacy manual prior to

administration. Part C is a single IV infusion study, and the enrollment of participants will not be linked to Part A and Part B enrollment.

In Parts A, B and C of the study, all participants will receive a single dose of sotrovimab on Day 1. Additionally, participants in Part A and Part B will need to complete a PRO assessment at home on Day 1, and will also need to complete a PRO assessment at the site on Days 2, 3, 5, and 8.

In all Parts, participants will need to return to the study site on Days 2, 3 and 5 and at Weeks 2, 3, and 4 (Day 29). At Weeks 8, 12, 20, and 24, the participants will need to return to the site or have a home visit. At Week 35, the participants in all Parts will have a phone call visit.
The study duration is 35 weeks after dosing. Participants can be screened up to 28 days before dosing; therefore, the maximum duration a participant will be in the study is 39 weeks.

Part A:

Part A is open-label and participants will be randomized in a 2:2:1:1 ratio to the following 4 treatment arms:

- 500 mg IM of 62.5 mg/mL sotrovimab administered into the dorsogluteal muscles
- 500 mg IM of 100 mg/mL sotrovimab administered into the dorsogluteal muscles
- 500 mg IM of 100 mg/mL sotrovimab administered into the anterolateral thigh muscles
- 500 mg IM of 100 mg/mL sotrovimab administered into the deltoid muscles

Approximately 190 participants will be enrolled assuming a 20% rate of non-evaluable participants to achieve approximately 150 evaluable participants across the 4 treatment arms. Therefore, the randomization ratio of 2:2:1:1 will result in approximately 63 participants randomized to each of the 62.5 mg/mL and 100 mg/mL dorsogluteal arms, respectively, and approximately 32 participants randomized to each of the 100 mg/mL anterolateral thigh and deltoid arms, respectively. Participants will be stratified by sex and 2 BMI strata (18 to ≤25 and >25 to 30 kg/m^2).

Part B:

Part B is optional and will consist of either 1 or 2 treatment arms (N=32/arm), as described under “Intervention Groups and Duration”.

Approximately 32 participants will be enrolled per treatment arm assuming a 20% rate of non-evaluable participants to achieve approximately 25 evaluable participants within each treatment arm.

If 2 treatment arms are opened in parallel in Part B, then participants will be equally randomized to both treatment arms. However, if only 1 treatment arm is opened for Part B or 2 treatment arms are opened sequentially, then participants will not be randomized. Participants will be enrolled to target a similar representation of sex and BMI groups with those from Part A.

Part B will allow assessment of 500 mg IM dose of 100 mg/mL and/or 62.5 mg/mL sotrovimab administered at the same and/or different injection volume/number of injections/sites of injections than those evaluated in Part A. Potential injection sites to be evaluated in Part B include deltoid, thigh, dorsogluteal, and/or ventrogluteal. An IA will be performed once half of the participants in Part A complete at least Day 8. The selection of treatment arms will be informed by the JSRT and the clinical study team after the IA. Part B will start enrolling participants once Part A has completed enrollment.

Part A and Part B:

The injection volume in the deltoid will not exceed 2.5 mL/injection. The injection volume in the gluteal muscles and thigh will not exceed 5 mL/injection. Follow-up will occur via site and home visits, and a phone call visit (as per the SoA, Section 1.3) for 35 weeks. Part A and Part B participants will receive a single 500 mg dose of sotrovimab for IM injection.

As an exploratory endpoint, this study will assess participant perception of the ISR, including pain (pain-NRS), bothersomeness of ISR, impact on sleep, impact on movement, and acceptability of the ISR (PIN_TS3.0 assessment).

For both Parts A and B, the JSRT will assess ISRs by reviewing data from a sentinel cohort. The sentinel cohort review will occur after all of the treatment arms within a study Part have approximately 5 participants who have completed at least Day 8. During review of the sentinel cohort, the JSRT will make one of the following decisions for each treatment arm:

- to continue enrollment in that treatment arm
- to stop enrollment in that treatment arm
- to have the dose administered using a lower volume of injection for that treatment arm by increasing the number of injections (e.g., 2 injections consisting of 2.5 mL instead of 1 injection consisting of 5 mL)
- to enroll an additional 5 participants in the treatment arm before making a decision.

The JSRT will also review safety data at regular intervals as described in the JSRT charter for both Parts A and B. Refer to Section 10.1.5 for details regarding the JSRT.

Evaluable participants are defined as those who have PK concentration data to allow estimation of the primary endpoints (i.e., AUCD1-29 and Cmax) and inclusion in the analysis.

Part C:

Part C is open-label, and participants will receive single IV infusion. Enough healthy participants will be screened to ensure approximately 200 participants (intend to target up to approximately 20 Japanese participants) are enrolled in Cohort 1 to receive a 3000 mg dose of sotrovimab infused over 60 minutes. Cohort 2 is optional and participants will receive a dose of up to 3000 mg infused over the time period to be specified in the pharmacy manual.

Part C participants will receive study intervention as sotrovimab (100 mg/mL) diluted for IV infusion. Refer to Section 6.1 and pharmacy manual for details. Cohort 1 and optional Cohort 2 enrollment are sequential.

Cohort 1:

- Initial dosing in this cohort will be staggered so that the first 2 participants will be considered sentinels and will be dosed 3000 mg sotrovimab administered intravenously at the same clinical trial site. After at least 24 hours (post dose), and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants will be dosed as non-sentinel participants.
- An in-stream safety lead-in data review will occur after approximately 30 participants have completed at least Day 8. JSRT will decide whether to continue with Cohort 1 and whether to proceed with Cohort 2 including the selection of dose and infusion rate. No dosing of further participants will take place until after the review is completed.
- Approximately 170 additional participants will then be enrolled into this cohort.
- An IA, including all data collected, will be conducted after approximately half of the participants in Cohort 1 complete at least Day 15 to support periodic data reviews across the program.

Cohort 2:

- A decision on whether to proceed with Cohort 2 including the selection of dose and infusion rate will be made by the JSRT and the clinical team based on the review of safety lead-in data from Cohort 1.
- Initial dosing in this cohort for the 2 sentinel participants will follow the same procedure as mentioned above in Cohort 1.

The JSRT will also review safety data at regular intervals as described in the JSRT charter for Part C. Refer to Section 10.1.5 for details regarding the JSRT.

Participants in Part C will be enrolled in the study for up to 28 days screening; will receive a single dose of sotrovimab on Day 1 at the study site; will return to the study site on Days 2, 3, and 5 and at Weeks 2, 3, and 4 (Day 29); will also return to the study site or have a home visit at Weeks 8, 12, 20 and 24; and will have an end-of-treatment follow-up period through 35 weeks.

Note: Enrolled means a participant's agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

4.2. Scientific Rationale for Study Design

This is a Phase 1 healthy participant study with 3 parts (Part A, an optional Part B, and Part C).

In addition to the current 62.5 mg/mL concentration, a 100 mg/mL ready-to-fill bulk drug substance, leveraging the same formulation, is being pursued in an effort to lower the injection volume when injected intramuscularly. This will allow additional injection sites to be used. The 100 mg/mL concentration is also being studied as an IV infusion.

Part A and an optional Part B of this study are open-label, parallel group, randomized parts, which will evaluate the safety, tolerability, and relative bioavailability of the 62.5 mg/mL concentration and the new 100 mg/mL concentration of sotrovimab following IM injections at different sites. Part A and Part B participants will receive a single 500 mg dose of sotrovimab for IM injection.

Part C is an open-label, single IV infusion study, which will characterize the safety and tolerability of 3000 mg sotrovimab in Cohort 1 and up to 3000 mg sotrovimab in an optional Cohort 2. Cohort 2 will be opened to potentially assess a different infusion rate and/or dose than Cohort 1.

Part A and Part B

An open-label design is chosen as the injections are given at different sites and different number of injections may be used. Given the open-label design, investigators, site study staff, and participants will not be blinded.

BMI and sex are principal determinants of parenterally administered mAb exposure. Therefore, in Part A, randomization to treatment arms will be stratified by sex and BMI to aim for a balance of strata between treatment arms. In Part B, participants will be enrolled to target similar representation of BMI and sex groups as in Part A.

The number of participants randomized to each treatment arm will provide acceptable precision for estimation of relative bioavailability. Due to the extended t1/2 of sotrovimab, 24 weeks is expected to provide sufficient duration to ensure the extrapolated portion of the AUC will be less than 20%.

Part C

The safety profile of sotrovimab has been evaluated at doses up to 2000 mg across the sotrovimab program, and there are no data to suggest that a 3000 mg dose may not demonstrate equivalent safety and tolerability. Based on preclinical toxicology studies, the margins for Cmax and AUC of the 3000 mg at the monkey NOAEL are 14.8× and 6.7×, respectively, providing a significant safety margin for the proposed dose. Taking these factors into account, it is considered that an open-label design is appropriate.

CCI [redacted]

4.3. Justification for Dose

The dose justification for the 500 mg dose (Part A and Part B) and the up to 3000 mg dose (Part C) are described below.

Parts A and B

A 500 mg IM dose of sotrovimab was selected for evaluation in Parts A and B of this study. A 250 mg and a 500 mg IM dose (dorsogluteal injection) are currently being evaluated in studies COMET-TAIL and COMET-PEAK. To date, in COMET-TAIL, 387 participants have been dosed with 500 mg IM sotrovimab (dorsogluteal injection). In COMET-TAIL, treatment with 500 mg IM sotrovimab was demonstrated to be non-inferior to 500 mg IV sotrovimab as measured by the proportion of study participants with mild or moderate COVID-19 progressing to >24 hours of hospitalization for acute management of any illness due to any cause or death through Day 29. The safety profile was also acceptable with a low rate of AEs in the 500 mg IM arm.

Part C

The proposed IV dose (up to 3000 mg) selected for Part C of this study was chosen to establish safety and tolerability across a range expected to encompass the intended clinical doses to be evaluated in treatment and prophylactic indications and be potential to cover future variants.

The NOAEL for VIR-7831 was 500 mg/kg, the highest dose tested, when VIR-7831 was administered via IV infusion once a week for 2 weeks in cynomolgus monkeys (TX-7831-0102). No IRRs were observed in the monkey toxicology study. Based on simulated Gen2 IV PK, the predicted AUCinf following a 3000 mg dose is 32,100 µg*day/mL and predicted Cmax is 912 µg/mL. Based on the proposed 3000 mg IV dose, the margins based on nonclinical Cmax and AUC at the monkey NOAEL are 14.8× and 6.7×, respectively.

In addition, sotrovimab (500 mg IV/IM) has been well-tolerated within the clinical program. While anaphylaxis and HSR have been observed in patients treated with sotrovimab, 1 patient in a study evaluating sotrovimab in patients hospitalized with COVID-19 had anaphylaxis reported, was treated, and recovered. Review of other mAbs clinical programs showed that proportion of HSRs was similar across treatment arms and did not occur more frequently in higher dose groups. Therefore, both the toxicity and clinical studies support the use of sotrovimab for the treatment of COVID-19 in accordance with the proposed dose regimen and intended indications.

4.4. 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.

A participant is considered to have completed the study if he/she completes the Week 35 visit.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age inclusive, at the time of signing the informed consent.
2. Participants must have received completed dose(s) in a SARS-CoV-2 vaccine series at the time of signing informed consent. Booster vaccines are permitted but not required.

Type of Participant and Disease Characteristics

3. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
4. Participants must be negative for COVID-19, determined by two consecutive negative results by any validated SARS-CoV-2 molecular test (e.g., RT-PCR on any respiratory type) separated by >24 hours. The first test may be carried out at any time during Screening, the second test will be at Day -1.
5. For Part C, inclusion in the Japanese subgroup analysis, a participant must meet all of the following criteria: Japanese ancestry, defined as being a descendant of 4 ethnic Japanese grandparents and 2 ethnic Japanese parents.

Weight

Body weight must be ≥40 kg considering BMI within the range of 18 to 30 kg/m^2.

Sex and Contraceptive/Barrier Requirements

6. Male and/or female.
7. Female participants must meet and agree to abide by the following contraceptive criteria. Contraception use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

  a. Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4: Contraceptive and Barrier Guidance.

  OR

b. Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least ~5 half-lives after the last dose of study intervention. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at Screening and on Day -1, before the first dose of study intervention. See Section 8.3.5 for Pregnancy Testing.

   – If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data.
2. Abnormal BP as defined as greater than 140 mm/Hg systolic, greater than 90 mm/Hg diastolic, or less than 90 mm/Hg systolic at Screening. BP at Screening is the average of 3 BP readings taken using the methods described in Section 8.3.2.
3. Known hypersensitivity to any constituent present in the investigational product or history of severe hypersensitivity or anaphylaxis after receiving a COVID-19 vaccine.
4. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment HSRs (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

5. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
6. For Part A and Part B, any condition that would prohibit receipt of IM injections in the investigator's opinion, such as coagulation disorder, bleeding diathesis, or thrombocytopenia.
7. Breast cancer within the past 10 years.
8. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN).
9. Total bilirubin >1.5 × ULN (isolated total bilirubin >1.5 × ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).
10. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
11. Participants exposed to an individual known to be infected with COVID-19 by PCR testing within the 14 days prior to Screening.
12. QT interval corrected using Fridericia's formula (QTcF) >450 msec.

Prior/Concomitant Therapy

13. Use of any over-the-counter or prescription medications within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing until completion of the follow-up visit, unless permitted in Section 6.8.
14. Treatment with biologic agents (such as mAbs including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.
15. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.
16. Receipt of any vaccine within 48 hours prior to enrollment.
17. Has received a SARS-CoV-2 vaccine but has not completed all doses in the series more than 28 days prior to Screening. SARS-CoV-2 vaccinations will not be allowed for 90 days after dosing.

Prior/Concurrent Clinical Study Experience

18. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56-day period.
19. Exposure to more than 4 new chemical entities (e.g., investigational pharmaceuticals) within 12 months prior to the first dosing day.
20. Enrollment in any investigational vaccine study within the last 180 days or enrollment in any other investigational drug study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer.
21. Current enrollment or past participation in this clinical study.

Diagnostic Assessments

22. Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to first dose of study intervention.
23. Positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
24. Positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
25. Positive pre-study drug/alcohol screen.
26. Positive HIV antibody test.

Other Exclusions

27. History of regular alcohol consumption within 6 months prior to the study defined as:
    - An average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
28. Regular use of known drugs of abuse.
29. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants should be fasting while arriving at the Screening Visit. Participants will be allowed to eat during the Screening Visit after the blood sample is drawn for clinical chemistry analysis.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 6 hours prior to Screening.
- Participants will abstain from alcohol for 24 hours prior to each visit to the clinic.
- Participants must have a negative drug test at screening and must abstain from recreational drug use from screening until after the final follow-up visit.

5.3.3. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants 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, any protocol deviations, and any SAEs.

If a participant fails any of the laboratory exclusion criteria, the test may be repeated once within the Screening period. If the participant fails the laboratory criteria for a second time, they will be considered a screen failure. Retesting within the screening window of any blood sample withdrawn due to sample handling problems, breakage or sample integrity is not considered a rescreening.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 2 times. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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.

6.1. Study Intervention(s) Administered

Table 3 Study Intervention(s) Administered

Intervention Label	Sotrovimab Injection, 62.5 mg/mL	Sotrovimab Injection, 100 mg/mL	Sotrovimab Infusion, 100 mg/mL	Sotrovimab Infusion, 100 mg/mL
Intervention on Label	VIR-7831	VIR-7831	VIR-7831	VIR-7831
Type	Biologic	Biologic	Biologic	Biologic
Dose Formulation	Solution in single use vial (62.5 mg/mL)	Solution in single use vial (100 mg/mL)	Solution in single use vial (100 mg/mL)	Solution in single use vial (100 mg/mL)

Unit Dose Strength(s)	62.5 mg/mL (500 mg/8 mL)	100 mg/mL (250 mg/2.5 mL)	100 mg/mL (250 mg/2.5 mL)	100 mg/mL (500 mg/5 mL)
Dosage Level(s)	500 mg (1 vial)	500 mg (2 vials)	Part C IV: Cohort 1 – 3000 mg (12 vials)	Part C IV Optional Cohort 2 – up to 3000 mg (up to 6 vials)
Route of Administration	IM injection	IM injection	IV infusion	IV infusion
Infusion Time	NA	NA	60 minutes	Sotrovimab dose and infusion time will be decided based on a safety review of Cohort 1 participants and will be specified in the pharmacy manual.
Use	Experimental	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor/designee	Provided centrally by the sponsor/designee	Provided centrally by the sponsor/designee	Provided centrally by the sponsor/designee
Packaging and Labeling	Study intervention will be provided in a single-use vial. Each single-use vial will be labeled as required per country requirement.	Study intervention will be provided in a single-use vial. Each single-use vial will be labeled as required per country requirement.	Study intervention will be provided in a single-use vial. Each single-use vial will be labeled as required per country requirement.	Study intervention will be provided in a single-use vial. Each single-use vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Sotrovimab, Xevudy, VIR-7831, GSK4182136	Sotrovimab, Xevudy, VIR-7831, GSK4182136	Sotrovimab, Xevudy, VIR-7831, GSK4182136	Sotrovimab, Xevudy, VIR-7831, GSK4182136

Table 4 Study Arms: Part A

Arm Title	**IM 62.5 mg/mL sotrovimab into dorsogluteal**	**IM 100 mg/mL sotrovimab into dorsogluteal**	**IM 100 mg/mL sotrovimab into anterolateral thigh**	**IM 100 mg/mL sotrovimab into deltoid**
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants will receive 500 mg sotrovimab via two 4 mL injections, one in each dorsogluteal muscle on Day 1.	Participants will receive 500 mg sotrovimab on Day 1. Injection volume in the dorsogluteal muscles will not exceed 5 mL/injection.	Participants will receive 500 mg sotrovimab on Day 1. Injection volume in the anterolateral thigh will not exceed 5 mL/injection.	Participants will receive 500 mg sotrovimab on Day 1. Injection volume in the deltoid will not exceed 2.5 mL/injection.
Associated Intervention Labels	Sotrovimab Injection, 62.5 mg/mL	Sotrovimab Injection, 100 mg/mL	Sotrovimab Injection, 100 mg/mL	Sotrovimab Injection, 100 mg/mL

Table 5 Study Arms: Part B

Arm Title	**Optional Arm 1**	**Optional Arm 2**
Arm Type	Experimental	Experimental
Arm Description	Participants will receive 500 mg of 100 mg/mL and/or 62.5 mg/mL sotrovimab on Day 1.	Participants will receive 500 mg of 100 mg/mL and/or 62.5 mg/mL sotrovimab on Day 1.
Associated Intervention Labels	Sotrovimab Injection, 100 mg/mL and/or 62.5 mg/mL	Sotrovimab Injection, 100 mg/mL and/or 62.5 mg/mL

The decision on the Part B treatment arms will be made as described in Section 4.1. Potential injection sites to be evaluated in Part B include deltoid, thigh, dorsogluteal, and/or ventrogluteal. Injection volume in the gluteal or thigh muscles will not exceed 5 mL/injection. Injection volume in the deltoid will not exceed 2.5 mL/injection.

Table 6 Study Cohorts: Part C

Cohort Title	**Cohort 1**	**Optional Cohort 2**
Cohort Type	Experimental	Experimental
Cohort Description	Participants will receive 3000 mg on Day 1	Participants will receive up to 3000 mg on Day 1
Associated Intervention Labels	Sotrovimab Infusion, 100 mg/mL diluted as per pharmacy manual	Sotrovimab Infusion, 100 mg/mL diluted as per pharmacy manual

Part A, Part B, and Part C:

Injections/infusions will be administered in the clinic with staff trained in emergency care and resuscitation procedures and an emergency care kit on hand during study intervention administration and post-therapy observation periods.

6.2. Preparation, Handling, Storage and Accountability

Instructions for the preparation of study intervention will be provided in a separate Pharmacy Manual.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols

or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or sponsor/designee study contact.

- A MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed on Day 1, as shown in the SoA (Section 1.3).

Part A:

In Part A, participants will be randomized 2:2:1:1 to receive

- 500 mg of 62.5 mg/mL sotrovimab administered into the dorsogluteal muscles,
- 500 mg of 100 mg/mL sotrovimab administered into the dorsogluteal muscles,
- 500 mg of 100 mg/mL sotrovimab administered into the anterolateral thigh muscles, or
- 500 mg of 100 mg/mL sotrovimab administered into the deltoid muscles, respectively.

Participants will be stratified by sex and 2 BMI strata (18 to ≤25 and >25 to 30 kg/m^2).

Part B:

In Part B, participants will receive a 500 mg IM dose of 100 mg/mL and/or 62.5 mg/mL sotrovimab. If two arms are opened in parallel in Part B, then participants will be equally randomized to both arms (N=32/arm). However, if Part B consists of just 1 treatment arm (N=32), or two arms opened sequentially (N=32/arm), then participants will not be randomized (N=32). Participants will be enrolled to target a similar representation of BMI and sex as in Part A. Enrollment into a specific sex and/or BMI group may be capped to achieve this target.

Part C

Part C will assess a single 3000 mg dose of IV sotrovimab in Cohort 1 and up to 3000 mg dose of IV sotrovimab in an optional Cohort 2 to investigate alternative dose and infusion rates in healthy participants. As Cohort 1 and Cohort 2 consist of just 1 treatment arm, participants will not be randomized.

Part A, Part B and Part C:

This is an open-label study; however, the specific intervention to be administered to a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will

record the intervention assignment on the applicable CRF, if required. Potential bias will be reduced by central randomization for Part A and Part B if 2 additional treatment arms are simultaneously recruited.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and administrations time of each injection will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

Dose modifications are not applicable for this study. See Section 7.1 for instructions to discontinue study intervention for safety reasons.

6.6. Continued Access to Study Intervention after the End of the Study

There will not be continued access to study intervention after the end of the study.

6.7. Treatment of Overdose

For this study, any dose of sotrovimab greater than the protocol-defined dose and frequency (one-time dose) will be considered an overdose.

No specific treatment is recommended for an overdose. The treating physician may provide supportive measures depending on the symptoms.

In the event of an overdose, the treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study 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.

Receipt of any investigational (not authorized or approved) SARS-CoV-2 vaccine is not permitted during the study. Receipt of any authorized or approved SARS-CoV-2 vaccine is not permitted following 90 days post-dosing per CDC guidelines (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html). Participants should consult with the primary investigator and their primary care physician on local guidelines for vaccine administration and guidance on the risks associated with administration of all vaccines while on study.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and Medical Monitor, the medication will not interfere with the study.

Paracetamol/acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

Pharmaceutical methods of contraception as described in Section 10.4.2 are permitted for use at any time during the study.

All prior and concomitant medication should be captured in the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1. Discontinuation of Study Intervention

A participant will be permanently discontinued from completion of drug infusion/injection if they experience a Grade 3 or higher systemic reaction (see Section 10.3 for AE grading).

If treatment intervention is permanently discontinued after a partial dose is received, the participant will remain in the study to be evaluated for follow-up safety assessments as indicated in the SoA (Section 1.3).

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. As this is a single-dose study, liver chemistry stopping criteria for a single participant are not applicable. Liver chemistry increased monitoring criteria will apply if participant's ALT is ≥ 3xULN and

are described in Section 10.5. Potential Hy's Law case (ALT≥3xULN AND total bilirubin ≥ 2xULN (>35% direct bilirubin) or INR >1.5) must be reported as SAE.

7.1.2. Temporary Discontinuation

For Part A and Part B: If a participant experiences a Grade 2 systemic reaction after the first injection, investigators will be instructed to pause prior to the second injection. A subsequent injection may be administered at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids).

For Part C: A participant will be temporarily discontinued from completion of drug infusion if they experience a Grade 2 (moderate) IRR, investigators will be instructed to pause the infusion. The infusion may subsequently resume at a slower pace at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids).

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor/designee may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, 12-lead ECG, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. The actual time of assessment or procedure must be reported in the eCRF.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- CCI [redacted]
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA (Section 1.3).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Typical blood volumes expected during the usual course of study participation will be approximately 150 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Screening Period

Informed consent must be obtained before conducting any study procedures. Screening will be performed no more than 28 days prior to randomization and include the assessments outlined in the SoA (Section 1.3).

8.1.1. Medical History

Relevant medical history within the last 3 years, as determined by the Investigator, should be reported. Details regarding history of medication, COVID-19 vaccination, drug, alcohol, and tobacco use will be reported. Details regarding illnesses (including COVID-19) and allergies, date(s) of onset, and whether condition(s) is currently ongoing will be collected for all participants and should be updated prior to dosing as indicated in the SoA (Section 1.3).

8.1.2. SARS-CoV-2 Testing

Participants will be tested for SARS-CoV-2 as outlined in the SoA (Section 1.3). The following criteria must be met for a participant to be included in this study:

- Two consecutive negative results by any validated SARS-CoV-2 molecular tests (e.g., RT-PCR on any respiratory type) separated by >24 hours [FDA, 2021]. The first test may be carried out at any time during Screening, the second test will be at Day -1

CCI [redacted].

8.2. Efficacy Assessments

Efficacy is not evaluated as a primary or secondary endpoint in this study; CCI [redacted].

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature (oral preferred), pulse rate (PR), oxygen saturation, respiratory rate (RR), and BP will be assessed.
- BP and pulse measurements will be assessed semi-supine or sitting with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded.

8.3.3. Electrocardiograms

ECGs will be obtained as described in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Electrocardiograms will be performed locally. Digital ECG waveforms will be archived centrally. Fridericia's correction formula will be used to determine the QTc. The review of the ECG printed at the time of collection must be documented.

Before the ECG test, the participant should be at rest for approximately 10 minutes. The participant should be in the semi-recumbent or supine position.

For triplicate 12-lead ECGs, each of the 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minutes) recording period.

8.3.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study (either at any timepoint as per SoA or any unscheduled assessment) should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Medical Monitor notified.

- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at Screening, on Day -1, and at Week 24 or at the Early Withdrawal Visit if a participant is withdrawn from the study prior to Week 24 during study intervention period.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6. Local Injection Site Tolerability

A local injection site tolerability assessment will be performed per the SoA (Section 1.3). Injection sites should be monitored for any AEs. Refer to Section 8.4.6 for assessment of AE severity.

At the discretion of the investigator, unscheduled visits are permitted as needed for follow up of any unresolved local injection site tolerability symptoms. Management guidelines for these symptoms are provided in Section 10.6.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

NOTE: GSK is acting on behalf of the Sponsor, Vir, for the purposes of global safety reporting for this study.

The definitions of AEs or SAEs can be found in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All AEs and SAEs will be collected from dose administration until Week 35 at the timepoints specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- All SAEs will be recorded and reported to GSK immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to GSK within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the 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 reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.4.7), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to GSK of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. GSK will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority IRBs/IECs, and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until Week 35.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant's pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate for 6 to 8 weeks after the date of delivery and the information will be forwarded to GSK.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to GSK as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Assessment of AE Severity

Standard toxicity grading according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) will be used to grade all AEs (refer to Section 10.3.3).

8.4.7. Adverse Events of Special Interest

Adverse events of special interest are defined in the study protocol as relevant known toxicities of other therapeutic mAbs or as a result of signals observed from previous studies in the nonclinical programs of sotrovimab that will be monitored by GSK either during or at the end of the study (through Week 35). These will be updated during the course of the study based on accumulating safety data.

Adverse event of special interest includes:

- HSRs occurring any time post dose
- IRRs within 24 hours post dose
- Injection site reactions

- Immunogenicity
- AEs potentially related to ADE of disease.

8.4.7.1. Injection-Related Reactions and Serious Hypersensitivity

Guidelines for monitoring relevant AEs encompassing hypersensitivity, angioedema and anaphylaxis as well as for the management of acute anaphylactic shock and minor allergic episodes will be in place at investigational sites. Investigators will be provided with general guidance on management of serious HSRs and such reactions will be managed appropriately per local guidelines/medical judgment. Pre-medications will be permitted at the investigator's discretion and will be appropriately documented.

8.4.7.2. Injection Site Reactions

Injections may be associated with local reactions (e.g., swelling, redness, pain). Study participants should be monitored after IM administration of study intervention for signs or symptoms of any ISRs as described in the SoA (Section 1.3). Local tolerability assessment is discussed in Section 8.3.6.

8.4.7.3. Immunogenicity

Therapeutic proteins, including mAbs, have the potential to induce an unwanted immune response (immunogenicity) in humans. This reaction leads to production of ADAs which may inactivate the therapeutic effects of the treatment and, in rare cases, induce AEs. This study will include participant follow-up for a period of 24 weeks to assess for the development of ADA and drug-neutralizing antibodies and potential impacts on safety, PK, and/or efficacy.

8.4.7.4. Antibody-dependent enhancement

This AESI is relevant to participants who are infected with COVID-19 after administration of study intervention. ADE of disease theoretically can occur via 1 of 3 previously described mechanisms:

- By facilitating viral entry into host cells and enhancing viral replication in these cells
- By increasing viral fusion with target host cells, enhancing viral replication in these cells
- By enhancing disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs.

The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations [Arvin, 2020]. This study will include participant follow-up for a period of 5 half-lives to assess for the potential of enhanced disease in the context of waning sotrovimab levels, which may manifest as an increased incidence of re-infection or increased severity of re-infections after recovery from initial illness. The third mechanism is hypothesized to occur at high levels of antigen (i.e., viral load) and antibody potentially leading to immune complex deposition and complement activation in tissue sites of high

viral replication. This may manifest as acute deterioration temporally associated with sotrovimab dosing or as increased severity or duration of illness in sotrovimab-treated participants vs. placebo-treated participants.

As of 10 March 2021, enrollment into the COMET-ICE study, evaluating sotrovimab for the treatment of non-hospitalized individuals with mild to moderate COVID-19, has been stopped based on the recommendation of IDMC. The total of 1057 participants have been randomized to either the IV infusion of sotrovimab Gen1 (500 mg dose) or placebo. Based on the Joint SRT review of blinded data, there has been no confirmed events of ADE. The ACTIV-3 TICO study of sotrovimab treatment in hospitalized participants with COVID-19 symptoms, which was terminated due to futility, did not reveal any safety concerns overall and no ADE. The COMET-TAIL study did not reveal any safety concerns overall and no ADE.

As described in Section 2.3.1, AEs potentially related to ADE of the disease will be reviewed by the JSRT to see if there are unusually severe manifestations of COVID-19 in treated individuals.

8.5. Pharmacokinetics

Blood samples for sotrovimab serum PK will be collected as detailed in the SoA (Section 1.3).

- Serum concentration time data for sotrovimab will be analyzed by non-compartmental methods.
- The actual collection date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of sotrovimab serum concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.
- At visits during which whole blood samples are collected to obtain serum endpoints other than PK sotrovimab, 1 sample of sufficient volume can be used.
- Instructions for the collection and handling of biological samples will be provided by the sponsor or designee.
- The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak serum concentrations) to ensure appropriate monitoring.

Serum PK concentrations will be listed and summarized by treatment arm and visit in the PK analysis set. Pharmacokinetic parameters will be computed using standard noncompartmental methods. Parameters may include, but are not limited to AUCD1-29, Cmax, Clast, Tmax, Tlast, AUCinf, AUClast, %AUCexp, t1/2, λz, Vz (IV), Vss (IV), CL (IV), V/F (IM), CL/F (IM).

As data permits other PK parameters in addition to the listed above may be calculated and will be listed and summarized using descriptive statistics. Definitions of PK parameters, methods for estimation and details of additional PK analyses will be included in the analysis plan.

CCI [redacted]

CCI [redacted]

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Antibodies to sotrovimab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to sotrovimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to sotrovimab and/or further characterize the immunogenicity of sotrovimab.

- The detection and characterization of antibodies to sotrovimab will be performed using a validated assay method by or under the supervision of the sponsor/designee. Samples collected for detection of antibodies to study intervention may also be evaluated for sotrovimab serum concentration as described in Section 8.5 to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. At visits during which serum samples for the determination of PK and immunogenicity of sotrovimab will be taken, 1 sample of sufficient volume can be used.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor/designee to enable further analysis of immune responses to sotrovimab.

CCI

[redacted]

8.11. Health Economics

Health economics parameters are not evaluated in this study.

8.12. Patient-reported Outcomes

8.12.1. Perception of Injection

Perception of Injection version 3 (PIN_TS3.0) will be used to assess the participant's perception of the injection across four dimensions (how bothersome ISRs are, impact on sleep, impact on movement, and the acceptability of ISRs) and 4 individual items (anxiety before injection, bothersomeness during injection, satisfaction with the injection system, and willingness to receive as a treatment).

PIN_TS3.0 is a 20-item questionnaire slightly modified from PIN version 1 for use in this study. PIN version 1 has been used previously in clinical trials studying ISR related to HIV treatment. PIN version 1 itself was adapted from VAPI questionnaire developed by Sanofi Pasteur, initially used for evaluating influenza vaccinations. Participants will provide a response for each PIN_TS3.0 item on a 5-point scale (1=most positive, 5=least positive). The timepoints for this assessment are provided in the SoA (Section 1.3). Paper PRO measures will be used in case ePRO is unavailable. Paper PRO will be brought to the site for data entry at the next visit.

8.12.2. Injection Site Pain

Pain-NRS will be used to assess the intensity of the pain at the injection site. Participants are asked to rate their pain at the injection site at this moment on an 11-point scale (0=No Pain, 10=Worst Pain Imaginable). Paper PRO measures will be used in case ePRO is unavailable. Paper PRO will be brought to the site for data entry at the next visit.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Part A:

The primary objectives are to estimate the relative bioavailability, safety, and tolerability of single-dose high-concentration sotrovimab administered intramuscularly in healthy participants. There are no formal statistical hypotheses planned.

Part B:

The secondary objectives are to estimate the relative bioavailability, safety, and tolerability of single-dose high-concentration sotrovimab administered intramuscularly in healthy participants. There are no formal statistical hypotheses planned.

Part C:

The primary objectives are to characterize the safety and tolerability of IV sotrovimab administered in healthy participants. There are no formal statistical hypotheses planned.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who entered the study. Note: screening failures (who never passed screening even if rescreened) are excluded from the Enrolled analysis set as they did not enter the study.
Randomized	All participants who were randomly assigned to study intervention. Data will be reported according to the randomized intervention.
Safety	All randomized participants who were exposed to study intervention. Participants will be reported according to the intervention they actually received.
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment – i.e., PK sample collected and analyzed. Note: Non-quantifiable [NQ] values will be considered as non-missing values. Participants will be reported according to the intervention they actually received.
PK Principal Stratum	All participants in the PK analysis set who would be able to complete the IM dose. Participants will be reported according to the treatment arm they actually received.

9.3. Statistical Analyses

9.3.1. General Considerations

The SAP will include a detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary and key secondary endpoints.

Modelling and analysis for Part A will be separate from the analysis for Part B, with only the 62.5 mg/mL IM formulation from Part A being included as the comparative arm for the analysis of Part B treatment arms.

For Part C, safety and PK data will be analyzed separately from Part A and Part B.

A JSRT will review safety data at regular intervals as described in the JSRT charter for Parts A, B, and C.

For both Parts A and B, the JSRT will assess ISRs by reviewing data from a sentinel cohort as described in Section 4.1. One of the decisions that can be made by the JSRT following review of safety data for the sentinel cohort would be to decrease the volume of each injection by increasing the number of injections. If the situation arises where the JSRT recommends the number of injections for the 100 mg/mL IM formulation at the dorsogluteal site is increased from 1 × 5 mL to 2 × 2.5 mL, PK data from all participants in the treatment arm will be combined and included in PK analyses. The same approach will be followed for secondary and exploratory endpoints.

For Part C, a subgroup analysis of Japanese participants will be further explored.

9.3.2. Primary Endpoint(s)/Estimands(s) Analysis

Part A

The co-primary objectives of this study are to assess relative bioavailability and safety profile of 100 mg/mL IM sotrovimab at the dorsogluteal injection site relative to the 62.5 mg/mL IM formulation administered dorsogluteally in participants through Day 29 regardless of initiation of prohibited medications. For the analyses planned in the following sections, a potential intercurrent event that will be considered is participants receiving an incomplete IM dose.

Events leading to missing data are participant withdrawal from study, lost to follow-up, or insufficient PK samples (determined per NCA analysis).

Only participants who have sufficient PK samples (determined per NCA analysis) to estimate $AUC_{D1\text{-}29}$ and C_{max} will be included in the PK parameter summaries. The concentration data of such participants will also be included in the PK concentration summaries. For participants who had incomplete dose, their available PK data will be only listed.

Part C

The primary objective of Part C of this study is to assess the safety profile of sotrovimab following administration of a single IV dose in participants through Day 29 regardless of initiation of prohibited medications. For the analyses planned in the following sections, a potential intercurrent event that will be considered is participants receiving an incomplete IV dose.

9.3.2.1. Pharmacokinetics

Table 7 Primary Estimand for Primary Pharmacokinetics Endpoint (Part A)

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years who would be able to complete the IM dose
Variable/Endpoints	Sotrovimab serum PK parameters: $AUC_{D1\text{-}29}$ and C_{max}
Treatment	100 mg/mL IM sotrovimab vs 62.5 mg/mL IM sotrovimab (dorsogluteal injections)
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving an incomplete IM dose. The strategy for handling this intercurrent event will be a Principal Stratum Strategy, where we are only interested in the strata of participants who would be able to receive a complete IM dose. Exclusion of participants who did not receive a complete IM dose will not introduce bias as the reasons for dose interruption are not related to their PK.
Population-Level Summary	The point estimate for the ratio of the geometric means of 100 mg/mL treatment group compared to the 62.5 mg/mL treatment group and the related 90% CI will be calculated.

Log-transformed parameters ($AUC_{D1\text{-}29}$ and C_{max}) will be compared between treatment groups using ANCOVA models that include all four treatment groups, sex, and BMI (in kg/m^2) as variables. Least square estimates of treatment differences (contrasts for each comparison of interest) will be back-transformed to estimate relative bioavailability with two-sided 90% CIs. This analysis will be based on the PK Principal Stratum Analysis Set. Further details will be included in the SAP.

9.3.2.2. Safety

Table 8 Primary Estimand of the Primary Safety Endpoint

Part A:

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years
Variable/Endpoints	Incidence of all AEs, SAEs, and AESI through Day 29 (i.e., all events on the database at the time of DCO)
Treatment	100 mg/mL IM sotrovimab and 62.5 mg/mL IM sotrovimab (dorsogluteal injections)
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving incomplete IM dose. The strategy for handling this intercurrent event will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included. Missing data will not be imputed.
Population-Level Summary	Frequency and percentages of participants

Part C Cohort 1:

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years
Variable/Endpoints	Incidence of all AEs, SAEs, and AESI through Day 29 (i.e., all events on the database at the time of DCO)
Treatment	Single IV infusion of sotrovimab at 3000 mg dose
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving incomplete IV dose. The strategy for handling this intercurrent event will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included. Missing data will not be imputed.
Population-Level Summary	Frequency and percentages of participants

For Part C optional Cohort 2, similar Estimand strategy will be followed for treatment: Single IV infusion of sotrovimab at up to 3000 mg dose.

Occurrence of AEs, SAEs, and AESIs will be displayed in the form of summaries and listings using the Safety population. Further details will be provided in the SAP.

9.3.3. Secondary Endpoint(s)

9.3.3.1. Pharmacokinetics

Table 9 Primary Estimand for Secondary Pharmacokinetics Endpoint (Part A)

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years who would be able to complete the IM dose
Variable/Endpoints	• $AUC_{D1\text{-}29}$ and C_{max} through Day 29 • AUC_{inf} through Week 24 • Serum PK of sotrovimab through Day 29 and Week 24
Treatment Conditions	• $AUC_{D1\text{-}29}$ and C_{max} through Day 29: 100 mg/mL sotrovimab (anterolateral thigh, deltoid) vs 62.5 mg/mL sotrovimab (dorsogluteal) • AUC_{inf} through Week 24: 100 mg/mL IM sotrovimab at three injection sites (dorsogluteal, anterolateral thigh, and deltoid) compared to the 62.5 mg/mL formulation administered dorsogluteally • Serum PK of sotrovimab through Day 29 and Week 24: 100 mg/mL and 62.5 mg/mL IM sotrovimab
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving an incomplete IM dose. The strategy for handling this intercurrent event will be a Principal Stratum Strategy, where we are only interested in the strata of participants who would be able to receive a complete IM dose. Exclusion of participants who did not receive a complete IM dose will not introduce bias as the reasons for dose interruption are not related to their PK.
Population-Level Summary	• $AUC_{D1\text{-}29}$ and C_{max} through Day 29: The point estimate for the ratio of the geometric mean of 100 mg/mL treatment group compared to the 62.5 mg/mL treatment group and the related 90% CI will be calculated • AUC_{inf} through Week 24: The point estimate for the ratio of treatment group geometric means and the related 90% CI will be calculated • Serum PK of sotrovimab through Day 29 and Week 24: geometric mean

The estimand strategy for secondary PK endpoints, including those for Part B, will be similar to the strategy described above; further details will be provided in the SAP.

Table 10 Primary Estimand for Secondary Pharmacokinetics Endpoint (Part C Cohort 1)

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years who would be able to complete the IV dose
Variable/Endpoints	• AUC_{D1-29} and Cmax through Day 29 • Serum PK of sotrovimab through Day 29 and Week 24
Treatment Conditions	• AUC_{D1-29} and Cmax through Day 29: Single IV infusion of sotrovimab at 3000 mg dose • Serum PK of sotrovimab through Day 29 and Week 24: Single IV infusion of sotrovimab at 3000 mg dose
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving an incomplete IV dose. The strategy for handling this intercurrent event will be a Principal Stratum Strategy, where we are only interested in the strata of participants who would be able to receive a complete IV dose. Exclusion of participants who did not receive a complete IV dose will not introduce bias as the reasons for dose interruption are not related to their PK.
Population-Level Summary	• AUC_{D1-29} and Cmax through Day 29: geometric mean • Serum PK of sotrovimab through Day 29 and Week 24: geometric mean

For Part C optional Cohort 2, similar Estimand strategy will be followed for treatment: Single IV infusion of sotrovimab at up to 3000 mg dose.

9.3.3.2. Safety

Table 11 Primary Estimand for Secondary Safety Endpoint (Part A and Part B)

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years
Variable/Endpoints	Incidence of all AEs, SAEs, and AESI through Day 29[a]/Week 35
Treatment	100 mg/mL IM sotrovimab administered at dorsogluteal, anterolateral thigh, and deltoid injection sites and 62.5 mg/mL IM sotrovimab administered dorsogluteally
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving incomplete IM dose. The strategy of handling this intercurrent event will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included. Missing data will not be imputed.
Population-Level Summary	Frequency and Percentages of participants

[a]Day 29 for anterolateral thigh and deltoid injection sites only as dorsogluteal injection sites are included in the primary safety endpoint.

Table 12 Primary Estimand for Secondary Safety Endpoint (Part C Cohort 1)

Primary Estimand	
Population	Male or female healthy participants aged 18 to 65 years
Variable/Endpoints	Incidence of all AEs, SAEs, and AESI through Week 35 (i.e., all events on the database at the time of DCO)
Treatment	Single IV infusion of sotrovimab at 3000 mg dose
Strategy for Intercurrent Events or Events Leading to Missing Data	The intercurrent event of interest is participants receiving incomplete IV dose. The strategy for handling this intercurrent event will be a Treatment Policy Strategy, where all safety data after the intercurrent event will be included. Missing data will not be imputed.
Population-Level Summary	Frequency and percentages of participants

For Part C optional Cohort 2, similar Estimand strategy will be followed for treatment: Single IV infusion of sotrovimab at up to 3000 mg dose.

9.3.4. Other Safety Endpoints

The estimand strategy for other safety endpoints, for all study parts, will be provided in the SAP.

9.3.5. Exploratory Endpoints

Further details of the analysis methods for the exploratory endpoints for all study parts will be provided in the SAP.

9.4. Interim Analysis

Part A and B:

In Part A and B, safety and tolerability data aggregated by treatment arm will be reviewed in-stream by the JSRT (see Section 10.1.5). A planned sentinel review will be conducted after approximately 5 participants per treatment arm complete at least Day 8 visit as described in Section 4.1.

Data from JSRT reviews may be used to inform study conduct or wider program decisions. These data will not be fully cleaned or undergo formal statistical analysis.

An IA will be conducted to review Part A data after approximately half of the participants in Part A complete at least Day 8 visit. The purpose of this interim is to inform the decision on whether to open Part B, and if needed the selection of treatment arms; further details of this IA will be specified in the SAP. Recruitment into Part A will continue with no pause at the time of the interim.

Thereafter, participants will continue to complete the remaining schedule of assessments as per the protocol.

Part C:

In Part C, aggregated safety and tolerability data will be reviewed in-stream by the JSRT (see Section 10.1.5). A planned in-stream review of safety lead-in data from Cohort 1 will be conducted after approximately 30 participants complete at least Day 8 visit as described in Section 4.1. The purpose of this review is to inform the decision to continue with Cohort 1 and whether to proceed with Cohort 2 including the selection of dose and infusion rate made by the JSRT and the clinical team. No dosing of further participants will take place until after the review is completed.

Data from JSRT reviews may be used to inform study conduct or wider program decisions. These data will not be fully cleaned or undergo formal statistical analysis.

An IA, including all data collected, will be conducted after approximately half of the participants in Cohort 1 complete at least Day 15, to support periodic data reviews across the program. Further details of this IA will be specified in the SAP.

Thereafter, participants will continue to complete the remaining schedule of assessments as per the protocol.

9.5. Sample Size Determination

Part A and B

The planned sample sizes for the number of evaluable participants in each treatment arm in Part A and Part B are based on precision estimation (using width of 90% CI) to assess the relative bioavailability. A sample size of approximately **50 evaluable participants** is selected for the 2 dorsogluteal arms in Part A (i.e., 500 mg IM of 62.5 mg/mL and 100 mg/mL sotrovimab arms, respectively) and approximately **25 evaluable participants** is selected for each of the 100 mg/mL sotrovimab thigh and deltoid arms in Part A and the 2 optional treatment arms in Part B. Therefore, the total number of evaluable participants planned in this study is **150 in Part A and 25 per treatment arm in Part B** (which may contain 1 or 2 treatment arms). To account for an expected 20% rate of non-evaluable participants approximately 190 participants will be randomized into Part A and 32 participants per/arm will be enrolled into Part B.

Sample size determinations are based on an assumed between participant coefficient of variation (CV_b) for $AUC_{D1\text{-}29}$, AUC_{inf}, and C_{max} of 50%.

For the primary PK objective, assuming a point estimate of 1 for the ratio of each **primary PK endpoints** (i.e., $AUC_{D1\text{-}29}$ and C_{max}) between the treatment arms under the variability assumptions and the planned sample size of evaluable participants described above, the 90% CIs are predicted to be:

Parameters	Treatment Comparison	Sample Size	CV_b	90% CI
AUC_{D1-29} and C_{max}	100 mg/mL sotrovimab dorsogluteal arm vs 62.5 mg/mL sotrovimab dorsogluteal arm	50 per arm	50%	(0.85, 1.17)

Similarly, for the secondary PK objective, assuming a point estimate of 1 for the ratio of each **secondary PK endpoints** (i.e., AUC_{D1-29}, AUC_{inf}, and C_{max}) between the treatment arms under the variability assumptions and the planned sample size of evaluable participants described above, the 90% CIs are predicted to be:

Parameters	Treatment Comparisons	Sample Size	CV_b	90% CI
AUC_{D1-29} and C_{max}	100 mg/mL sotrovimab anterolateral thigh or deltoid arm vs 62.5 mg/mL sotrovimab dorsogluteal arm	25 vs 50	50%	(0.80, 1.25)
AUC_{inf}	100 mg/mL sotrovimab dorsogluteal arm vs 62.5 mg/mL sotrovimab dorsogluteal arm	50 per arm	50%	(0.85, 1.17)
AUC_{inf}	100 mg/mL sotrovimab anterolateral thigh or deltoid arm vs 62.5 mg/mL sotrovimab dorsogluteal arm	25 vs 50	50%	(0.80, 1.25)

Part C

The planned sample size for the number of evaluable participants in Part C Cohort 1 is 200. With 200 participants (intend to target up to approximately 20 Japanese participants), there is a 90% chance of observing at least 1 AE of interest, if the true incidence rate of that AE is not below 1.14%. Of note, in COMET-ICE, the IRR rate was 1.14%. The sample size has been selected to provide sufficient safety and tolerability data to evaluate the higher IV dose of sotrovimab proposed for this part.

Part C Cohort 2 will be considered optional and will be opened following safety lead-in review based on Part C Cohort 1 data. The planned sample size for the number of evaluable participants in Part C Cohort 2 is 50. With 50 participants, there is a 90%

chance of observing at least 1 AE of interest, if the true incidence rate of that AE is not below 4.5%. Cohort 2 will supplement the data from Cohort 1 and may be combined at the end of study if the same dose is administered in both cohorts.

The precision of event rate estimation is shown in the table below, as indicated by the width of 95% CIs. More specifically, the total number of 250 participants reflects the precisions when summarizing over both the cohorts at the end of study if the same dose is administered.

Precision of Estimated Event Rate:

Total Number of Participants	**Observed Event Rate**	**Number of Participants with a Particular Event Observed**	**95% CI**
200 (individual study size for Part C Cohort 1)	0.5%	1	(0.01%, 2.75%)
	1.0%	2	(0.12%, 3.57%)
	2.0%	4	(0.55%, 5.04%)
	5.0%	10	(2.42%, 9.00%)
	10.0%	20	(6.22%, 15.02%)
	50.0%	100	(42.87%, 57.13%)
50 (individual study size for Part C Optional Cohort 2)	0.5%	1	(0.05%, 10.65 %)
	1.0%	1	(0.05%, 10.65%)
	2.0%	1	(0.05%, 10.65%)
	5.0%	3	(1.25%, 16.55%)
	10.0%	5	(3.33%, 21.81%)
	50.0%	25	(35.53%, 64.47%)

Total Number of Participants	**Observed Event Rate**	**Number of Participants with a Particular Event Observed**	**95% CI**
250 (combined study size for Part C Cohort 1 and Optional Cohort 2 if dose is the same)	0.5%	2	(0.10%, 2.86%)
	1.0%	3	(0.25%, 3.47%)
	2.0%	5	(0.65%, 4.61%)
	5.0%	13	(2.80%, 8.73%)
	10.0%	25	(6.58%, 14.41%)
	50.0%	125	(43.63%, 56.37%)

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:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
    - Applicable ICH GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - 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/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor/designee with sufficient, accurate financial information as requested to allow the sponsor/designee 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.
- 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 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.
- 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.
- Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about sotrovimab or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have sotrovimab approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor/designee. Any participant records or datasets that are transferred to the sponsor/designee will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor/designee in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor/designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Joint Safety Review Team

A JSRT comprised of team members from clinical research, global safety, and statistics from GSK and Vir, will review safety data throughout the study from all participants. The responsibilities of the JSRT and frequency of assessments will be outlined in the JSRT charter. The JSRT will review safety data from a sentinel cohort for each study Part and will review Part A data to inform Part B decisions, as described in Section 4.1. Additionally, the JSRT will review safety lead-in data from Part C Cohort 1 to decide to continue with Cohort 1 and whether to proceed with Cohort 2 (with a selection of different dose and infusion rate than Cohort 1). JSRT may request additional data before making a decision.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- The sponsor or designee will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with the sponsor/GSK Policy.
- The sponsor/GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless 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 physically or electronically signing the CRF.

- Guidance on completion of CRFs will be provided in eCRF completion guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the Data Surveillance Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- 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 including definition of study critical data items and processes (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 for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent contract research organization (CRO) document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary 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.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or 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. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. 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 GSK or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's/designee's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor/designee shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. 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: Clinical Laboratory Tests

- The tests will be performed by central or local laboratory and the details are described in Table 13.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Coagulation	International normalized ratio (INR)	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT)	
Clinical Chemistry[1]	Blood urea nitrogen	Potassium	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (fasting at Screening and non-fasting at all other timepoints)	Calcium	Total blood/serum alkaline phosphatase[2]	
Urine Testing	• Routine Urinalysis o Specific gravity o pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick o Microscopic examination (if blood or protein is abnormal) • Urine creatinine and urine albumin			
Pregnancy testing	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)[3]			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in WOCBP only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, marijuana and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a 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 a study intervention.

• **Definition of Unsolicited and Solicited AE**
• An unsolicited AE is an AE that was not solicited using a participant diary or form with pre-specified criteria. Unsolicited AEs are obtained either by asking a general question or unprompted by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned.

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 condition 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 intervention- intervention 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 NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (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 AE. If a complication prolongs hospitalization or fulfils 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.
d. Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. 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 to GSK.

- 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.

Assessment of Intensity

Standard toxicity grading according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.1 (July 2017) will be used to grade all AEs.

Table 14 should be used to grade the severity of an AE that is not specifically identified in the grading tables within *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.1 (July 2017). In addition, all deaths related to an AE are to be classified as Grade 5.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE as per Section 10.3.2, NOT when it is rated as severe.

Table 14 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Not Otherwise Specified in DAIDS version 2.1

PARAMETER	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Clinical AE **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- 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.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE 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 GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool 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) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (at least 1 week apart) is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

a) Documented hysterectomy
b) Documented bilateral salpingectomy
c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (at least 1 week apart) is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable

Sexual abstinence

- *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver Chemistry Monitoring Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Monitoring Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND total bilirubin≥ 2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report to GSK as an SAE[1,2].</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column.
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)
MONITORING:
If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND total bilirubin < 2xULN and INR ≤1.5:
• Perform liver chemistries (include ALT,</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within 168 days after the most recent dose[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gammaglutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications.
• Record alcohol use on the liver event alcohol intake form</td></tr>
</table>

Liver Chemistry Monitoring Criteria	
AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct assay should be done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable**, record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported to GSK as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.

3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the dose of study intervention prior to PK blood sample draw. Instructions for sample handling and shipping are in the SRM.

10.6. Appendix 6: Management of Local Injection Site Reactions and Systemic Symptoms (Anaphylaxis)

A. Local Injection Site Reactions

Signs and Symptoms	Management
Redness, soreness or swelling at the injection site	Apply a cold compress to the injection site(s) Consider giving an analgesic (e.g., ibuprofen, acetaminophen, paracetamol)
Itching and redness	Consider giving an anti-pruritic (e.g., diphenhydramine) Observe patient closely for the development of generalized symptoms
Slight bleeding	Apply pressure and an adhesive compress
Continuous bleeding	Place gauze pads over the site and maintain direct and firm pressure

If a participant has evidence of necrosis/ulceration, the participant should be referred to a higher level of acute care (e.g., hospital Emergency Department) for appropriate management.

B. Systemic Reactions/Anaphylaxis

As with any antibody, allergic reactions to study intervention are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Diagnosis of Anaphylaxis

The most common signs and symptoms of anaphylaxis are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritis). However, 10-20% of patients have no skin findings.

Danger Signs include:

- Rapid progression of symptoms
- Evidence of respiratory distress (stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis)
- Vomiting
- Abdominal pain
- Hypotension
- Dysrhythmia
- Chest pain
- Collapse

Management of Anaphylaxis

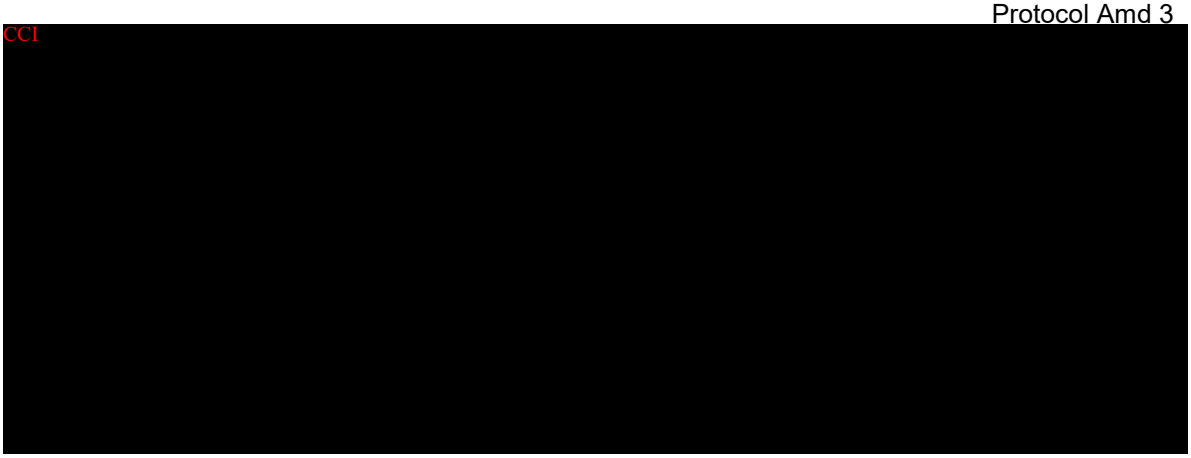
The following procedures should be followed in the event of a suspected anaphylactic reaction:

1. Call for additional medical assistance; activate emergency medical services
2. Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry
3. First-line treatment:
    - Administer epinephrine (1.0 mg/mL) aqueous solution (1:1000 dilution) – 0.5 mg (0.5 mL) IM in the anterolateral thigh
    - If using an epinephrine auto-injector – use 0.3 mg IM into the anterolateral thigh
    - May be repeated every 5 to 15 minutes up to 3 times
4. Optional treatment (antihistamine):
    - Diphenhydramine 50 mg oral/IV/IM
      OR
    - Hydroxyzine 25 mg oral/IM
5. Give oxygen (8-10 L/minute) via facemask, as needed
6. Normal saline rapid bolus – treat hypotension with rapid infusion of 1 to 2 liters IV
7. Monitor patient until emergency medical services arrive.

References

1. Medical Management of Vaccine Reactions in Adults in a Community Setting, Immunization Action Coalition, https://www.immunize.org/catg.d/p3082.pdf. Accessed May 27, 2021.
2. Preventing and Managing Adverse Reactions, General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Centers for Diseases Control and Prevention website. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html. Accessed May 27, 2021.
3. Sampson HA Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391-7.

CCI



10.8. Appendix 8: Abbreviations and Definitions and Trademarks

Term	Definition
λz	Terminal elimination rate constant
%AUCexp	Area under the plasma concentration-time curve extrapolated from time to infinity as a percentage of total AUC
Ab	Antibody
ADA	Anti-drug antibodies
ADE	Antibody-dependent enhancement
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCD1-29	Area under the serum concentration-time curve, from Day 1 to Day 29
AUCinf	Area under the serum concentration-time curve from time zero to infinity
AUClast	Area under the serum concentration-time curve from time zero to time of last measurable concentration
BMI	Body mass index
BP	Blood pressure
Clast	Last measurable serum concentration
Cmax	Maximum observed concentration
CA	Competent Authority
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance following extravascular route of administration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CV_b	Coefficient of variation
DAIDS	Division of Acquired Immune-Deficiency Syndrome
DCO	Data cut-off

Term	Definition
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
EC	Ethics Committee
EC50	Half maximal effective concentration
EC90	90% effective concentration
ECG	Electrocardiogram
EoS	End of study
eCRF	Electronic case report form
ePRO	Electronic device for participants to complete patient-reported outcome measure
EUA	Emergency use authorization
F	Bioavailability
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
Gen2	Generation 2
GCP	Good clinical practice
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
HSR(s)	Hypersensitivity reaction(s)
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
ICU	Intensive care unit
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgG1κ	Immunoglobulin G1 kappa
IM	Intramuscular

Term	Definition
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRR(s)	Infusion-related reaction(s)
ISR(s)	Injection site reaction(s)
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JSRT	Joint Safety Review Team
LS	Fc modification
mAb	Monoclonal antibody
MCH	Mean corpuscular volume
MCV	Mean corpuscular hemoglobin
MSDS	Material Safety Data Sheet
NCA	Non-compartmental analysis
NI	Non-inferiority
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
NOAEL	No-observed-adverse-effect-level
Pain-NRS	Injection site pain numeric rating scale
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PI	Principal investigator
PIN_TS3.0	Perception of Injection version 3
PK	Pharmacokinetic(s)
PR	Pulse rate
PRO	Patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
QTLs	Quality tolerance limits
RNA	Ribonucleic acid
RR	Respiratory rate
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE(s)	Serious adverse event(s)

Term	Definition
SAP	Statistical Analysis Plan
SARS-CoV-1	Severe acute respiratory syndrome coronavirus-1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SoA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Terminal elimination half-life
Tlast	Time of the last quantifiable concentration
Tmax	Time to reach Cmax
ULN	Upper limit of normal
UK	United Kingdom
US	United States
V	Variance
V/F	Apparent volume of distribution following extravascular route of administration
Vz	Apparent volume of distribution during the elimination phase
Vss	Apparent volume of distribution at steady state
VAPI	Vaccines Perception of Injection Questionnaire
Vir	Vir Biotechnology, Inc.
VOC(s)	Variant(s) of concern
VOI(s)	Variant(s) of interest
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Trademark Information

Trademarks of the GSK group of companies
Xevudy

Trademarks not owned by the GSK group of companies
None

10.9. Appendix 9: Protocol Amendment History

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 2	06-SEP-2022	TMF-14575517
Amendment 1	01-FEB-2022	TMF-14439761
Original Protocol	13-DEC-2021	TMF-14082482

Amendment 2: 06-SEP-2022

This amendment is considered to be substantial based on the description of change and rationale mentioned in the below table.

Overall Rationale for the Amendment: The protocol has been amended to include Part C to the study design to characterize the safety and tolerability of single IV infusion of sotrovimab in Cohort 1 and an optional Cohort 2.

Section # and Name	Description of Change	Brief Rationale
Section 1: Protocol Summary Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities (SoA) Section 2: Introduction Section 2.1 Study rationale Section 3: Objectives and Endpoints Section 4: Study Design Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 4.3 Justification for Dose Section 4.4 End of Study Definition Section 9: Statistical Considerations	Updated the rationale in the synopsis and study rationale sections as per the recent information available on sotrovimab development and authorization. Added the rationale and design of Part C in various sections of the protocol where applicable. Part C will be open-label, wherein participants will receive a single 3000 mg dose of IV sotrovimab in Cohort 1 and up to 3000 mg dose of IV sotrovimab in an optional Cohort 2. The rationale for conducting this part and the number of participants considered for Part C is explained across the synopsis and overall design sections. Added the language for in-stream safety lead-in data review at Day 8, and also modified the JSRT review language for Part C in Synopsis and JSRT charter. Added a new Schema and SoA table for Part C, which describes the design, treatment duration, visit frequency and study assessments. Added new Part C objectives and endpoints.	To characterize the safety and tolerability of IV sotrovimab and to potentially explore further IV doses of sotrovimab and/or alternative infusion rates. The proposed range of IV doses/infusion rates was chosen to support clinical doses for potential future clinical studies.
Section 2.2 Background	Updated the number of COVID-19 cases and associated deaths reported globally and in the US. Added Omicron BA.2 virus information with fold change in EC50 and EC90 values. Added Omicron BA.4 and Omicron BA.5 virus information with fold change in EC50 values.	New information available.
Section 2.2.1 Clinical Experience with Sotrovimab	Included information from the RECOVERY Trial, COMET-TAIL safety sub-study and PROTECT-V study.	To evaluate the safety and tolerability of IV sotrovimab at 1000 mg and 2000 mg at different study population.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment table Section 2.3.2 Benefit Assessment Section 2.3.3 Overall benefit: Risk Conclusion	Included IRR and ADE information and made updates related to Parts A, B and C in all the applicable risks described in risk assessment table. Updated these sections with the recently available information on sotrovimab and also included Part C, which may support options for therapeutics and effective preventive measures.	New and relevant information available for IRRs, ADE, ISR and HSRs, and for Parts A, B, and C.
Section 3 Objectives and Endpoints	Added new Part C objectives and endpoints. Updated primary estimand for Part C.	New and relevant safety primary estimand information available for Part C.
Section 4.2 Scientific Rationale for Study Design	Added data from preclinical toxicology studies to support Part C design.	Information added to support Part C design.
Section 4.3 Justification for Dose	Added data from preclinical toxicology studies to support Part C design. CCI [redacted]	CCI [redacted]
Section 5.1 Inclusion Criteria	Added an inclusion criterion to define the type of participant and disease characteristics in Japanese population.	Updated relevant information to align with Part C enrollment.
Section 5.2 Exclusion Criteria	Updated the medical condition for HSR.	New and relevant information available.
Section 6.1 Study Intervention(s) Administered table	Added sotrovimab dose information for Part C. Included study arms table for Part C.	New and relevant information available for Part C.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Added information regarding the design and conduct of Part C.	New and relevant information available for Part C.
Section 7.1 Discontinuation of Study Intervention Section 7.1.2 Temporary Discontinuation	Updated the criteria for permanent and temporary discontinuation of study intervention.	Relevant information available for Part C.
CCI [redacted]		
Section 8.2 Efficacy Assessments	Updated the language of the efficacy assessment to align with Part C design.	New and relevant information available for Part C.

Section # and Name	Description of Change	Brief Rationale
Section 8.4.7 Adverse Events of Special Interest Section 8.4.7.1 Injection-Related Reactions and Serious Hypersensitivity Section 8.4.7.2 Injection Site Reactions Section 8.4.7.4 Antibody-dependent Enhancement	Updated the language of these sections to align with Part C design. Added ADE as a new AESI in Section 8.4.7.	New and relevant information available for Part C.
Section 8.5 Pharmacokinetics	Updated the PK parameters.	New and relevant information available.
CCI [redacted] CCI		
Section 9.1 Statistical Hypotheses Section 9.3 Statistical Analyses Section 9.4 Interim Analysis Section 9.5 Sample Size Determination	Updated the text in the sub-sections of the protocol listed to the left column to add clarity and rationale for the data analysis that will be performed for Part C.	New and relevant information available for Part C.
Section 10.1.5 Committees Structure	Added additional text to the JSRT charter to include Part C review.	New and relevant information available for Part C.
Throughout document	Minor editorial updates, formatting and stylistic changes are made to align the content with the newly added information of Part C.	Updates are made to maintain consistency, for better clarity, and to improve readability.

Amendment 1: **01-FEB-2022**

This amendment is considered to be substantial based on the description of change and rationale mentioned in the below table.

Overall Rationale for the Amendment:

Based on Food and Drug Administration (FDA) feedback, protocol changes were made to add an additional pharmacokinetics (PK) blood sample collection on Day 5 for better characterization of the absorption phase of intramuscular (IM) sotrovimab and to extend the safety follow-up through Week 35 (~5 half lives of sotrovimab).

Section # and Name	Description of Change	Brief Rationale
Section 1: Protocol Summary 1.1 Synopsis 1.3 Schedule of Activities (SoA) Section 2: Introduction 2.3.1 Risk Assessment table Section 4: Study Design 4.1 Overall Design	Added a Day 5 on-site visit that includes brief physical examination, vital signs, local injection site tolerability assessment, safety laboratory assessments, and PK blood sample. The patient-reported outcome (PRO) assessments which were going to be performed at home will now occur at the site visit.	Changes made to include a PK blood sampling visit on Day 5. Since the Day 5 PK blood sampling requires a site visit, other Day 5 assessments were updated.
Section 1: Protocol Summary 1.1 Synopsis 1.2 Schema 1.3 SoA Section 3: Objectives and Endpoints Section 4: Study Design 4.1 Overall Design 4.4 End of Study Definition Section 5: Study Population 5.1 Inclusion Criteria Section 8: Study Assessments and Procedures 8.4.1 Time Period and Frequency for Collecting AE and SAE Information 8.4.5 Pregnancy 8.4.7 Adverse Events of Special Interest Section 9: Statistical Considerations 9.3.3.2 Safety 9.4 Interim Analysis	Added a phone call visit at Week 35 to capture AEs, SAEs, AESI and pregnancy status. Extended the safety follow-up period through Week 35. Added instructions for all WOCBP to continue contraception through Week 35.	Given that the half-life of sotrovimab is approximately 48.8 days, a decision was made to extend the safety follow-up through Week 35 (~5 half-lives of sotrovimab).
Section 1: Protocol Summary 1.1 Synopsis Section 4: Study Design 4.1 Overall Design	Added the maximum duration a participant will be in the study as 39 weeks	Change made due to extension of safety follow-up period through Week 35

Section # and Name	Description of Change	Brief Rationale
Section 1: Protocol Summary 1.1 Synopsis 1.2 Schema Section 2: Introduction 2.1 Study Rationale Section 3: Objectives and Endpoints Section 4: Study Design 4.1 Overall Design 4.2 Scientific Rationale for Study Design Section 6: Study Intervention(s) and Concomitant Therapy 6.1 Study Intervention(s) Administered: Table 3, Study Arms – Part B 6.3 Measures to Minimize Bias: Randomization and Blinding	Added the 62.5 mg/mL concentration as an option in Part B of this study	The 62.5 mg/mL concentration was added as an option in Part B to align with Part A
Section 2: Introduction 2.2 Background 11 References	Updated the background on Emergency Use Authorization (EUA) for SARS-CoV-2 mAbs and included a new reference and deleted 3 old references	Updated to align with FDA EUA updates, January 2022
Section 1: Protocol Summary 1.1 Synopsis Section 4: Study Design 4.1 Overall Design Section 9: Statistical Considerations 9.4 Interim Analysis	Updated the text in Section 9.4 (Interim Analysis) to add clarity and rationale for the data analysis that will be performed once half of the participants in Part A complete at least Day 8	To improve clarity and readability
Section 1: Protocol Summary 1.3 SoA	Added additional hematology laboratory assessments on Day 2, 5, 8, and 29	Expanded laboratory assessments to include further hematology assessments in addition to baseline
Throughout document	Other minor edits, formatting and typographical corrections are made	To improve readability

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