Statistical Analysis Plan Amendment 4

Study ID: 218128

Official Title of Study: 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

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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
Study Number:	218128 (VIR-7831-5012 COSMIC)
Compound Number:	Sotrovimab (also known as Xevudy, GSK4182136, VIR-7831)
Abbreviated Title:	Relative bioavailability, safety, and tolerability of single-dose sotrovimab injection in adults

Sponsor Name: This study is sponsored by VIR Biotechnology, Inc. GlaxoSmithKline is supporting VIR Biotechnology, Inc. in the conduct of this study

Regulatory Agency Identifier Number(s)

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	15 Mar 2022	Amendment (01Feb2022) GlaxoSmithKline Document Number TMF-14439761]	N/A	Original Version
Amendment 1	11 Oct 2022	Amendment 2 (06Sep2022) GlaxoSmithKline Document Number TMF-14575517]	Added Part C (single IV dose of sotrovimab) related contents to original SAP	With the addition of Part C to the study design in Protocol Amendment 2, safety and tolerability assessment of Part C Cohort 1 and evaluation of COVID-19 treatment and prophylactic indications will be performed.
Amendment 2	25 Jan 2023	Amendment 2 (06Sep2022) GlaxoSmithKline Document Number TMF-14575517]	Definition of enrolled population for Part C to SAP Amendment 1. Common (≥ 1%) AEs, common (≥ 1%) Non-Serious AEs, common (≥ 1%) SAEs for Part C. Subgroup analysis for Japanese Participants.	New Enrolled analysis set as Part C is not randomized. To report the incidence additionally at 1% threshold. Specific Japanese participant Subgroup

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				analysis need to be prespecified.
			Sample Size precision estimate for n=100 Interim Analysis.	To check the precision at n=100 for the planned Interim Analysis.
Amendment 3	17 Nov 2023	Amendment 3 (30Mar2023) GlaxoSmithKline Document Number TMF-15739935]	Added the infusion time to administer single dose of IV sotrovimab in Part C Cohort 1 CCI [redacted]	Alignment with the Protocol Amendment 3
			Added the descriptions of handling of triplicates ECGs measurement at post baseline in Section 4.1.2.	
			CCI [redacted]	
			Updated the intercurrent	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			events for the Efficacy Assessment Added the derivation of the Worst-case post-baseline for QTcF values Removed reference to the wording regarding the pausing of Part C Cohort 1 recruitment at time of interim	
Amendment 4		Amendment 3 (30Mar2023) GlaxoSmithKline Document Number TMF-15739935]	Updated text for reporting of AESIs (Immunogenicity and AEs potentially related to antibody-dependent enhancement of disease)	AESIs: Immunogenicity related AEs and AEs potentially related to antibody-dependent enhancement of disease do not have specific MedDRA SMQs or custom list of PTs to programmatically select events matching these categories of AESIs.

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report(s) (CSR) for Protocol 218128.

This SAP covers the analyses planned for the following Statistical Analysis Complete (SAC) deliverables:

- Part A Interim Analysis (IA)
- Part A Day 29
- Part A Week 24
- Part A Week 35
- Part C Cohort 1 IA
- Part C Cohort 1 Day 29
- Part C Cohort 1 Week 24
- Part C Cohort 1 Week 35

At the time of writing this SAP, an optional Part B or optional Part C Cohort 2 has not been confirmed. Under the condition that Part B or Part C Cohort 2 is required, a SAP amendment will be created to include Part B or Part C Cohort 2. Details of the planned analyses are provided in Section 4.7.

Note that in line with the guidelines, this SAP will use the term "participant", while all data displays (Tables, Figures & Listings [TFL]) produced as part of the planned dry-run and the SAC, will use the term "subject" which reflects GlaxoSmithKline (GSK) Data Display Standards terminology.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
Pharmacokinetics **<u>Part A:</u>** 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 pharmacokinetics (PK) parameters: $AUC_{D1\text{-}29}$ and Cmax
Safety **<u>Part A:</u>** To evaluate the safety and tolerability profile of 100 mg/mL IM sotrovimab and	Incidence of all adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESI) through Day 29

Objectives	Endpoints
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 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 C:** To characterize the PK of IV sotrovimab in Cohort 1 through Day 29	Sotrovimab PK parameters: AUC_{D1-29} and C_{max}
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	Sotrovimab PK parameter: AUC_{inf}
Pharmacokinetics **Part A:** To characterize the PK of 100 mg/mL and 62.5 mg/mL IM sotrovimab through Day 29 and Week 24	Serum PK of sotrovimab

Objectives	Endpoints
Part C: To characterize the PK of IV sotrovimab in Cohort 1 through Day 29 and Week 24	
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 C:** To evaluate the safety and tolerability profile of IV sotrovimab in Cohort 1 through Week 35	**Part A:** Incidence of AEs, SAEs, and AESI through Day 29/Week 35 **Part C:** Incidence of AEs, SAEs, and AESI through Week 35
Other Safety	
Part A: 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 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) Evaluate the pain, ISR, and acceptability of both the 62.5 mg/mL and 100 mg/mL	• Totally acceptable or very acceptable pain and totally acceptable or very acceptable local reaction

Objectives	Endpoints
formulations of sotrovimab administered intramuscularly	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 • 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: $AUC_{D1\text{-}29}$ and C_{max}.
- 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% confidence interval (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 data cut-off [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?

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.
- 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.

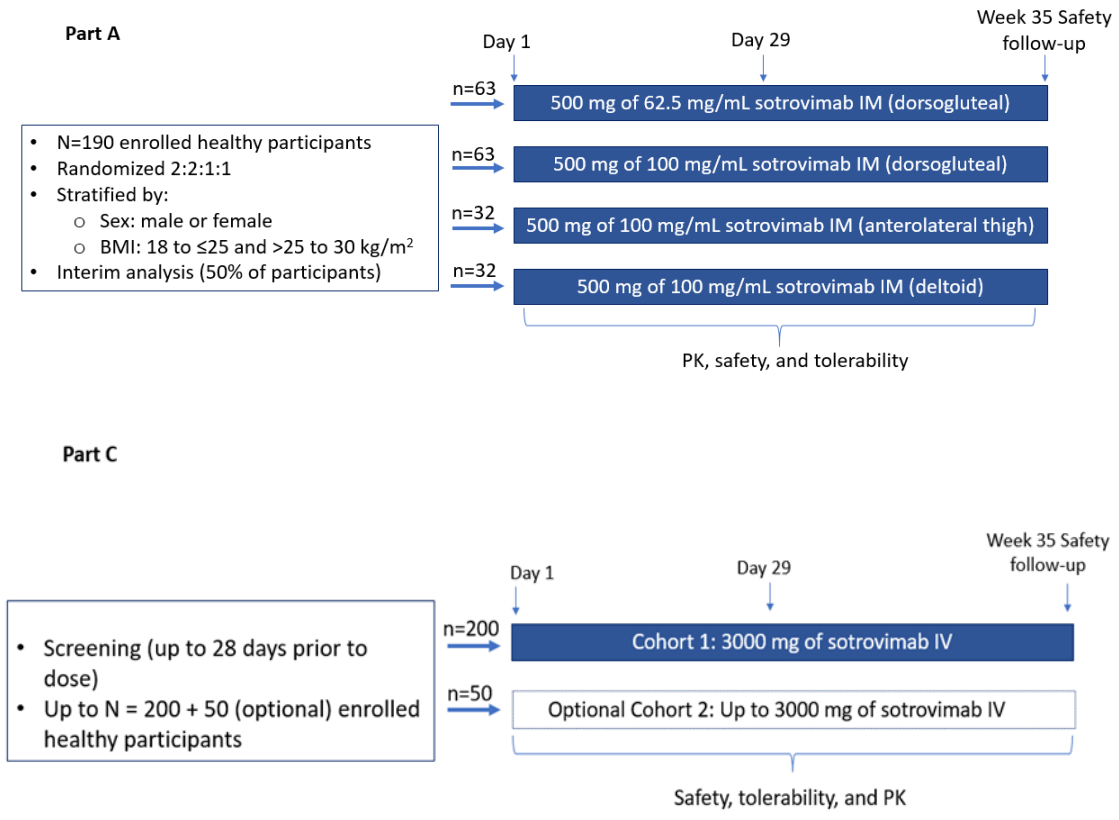
Rationale for Estimands:

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.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	This is 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.

Overview of Study Design and Key Features	
	Part A: On Day 1, participants will be randomized in a 2:2:1:1 ratio to the following four treatment arms: o 500 mg IM of 62.5 mg/mL sotrovimab administered into the dorsogluteal muscles o 500 mg IM of 100 mg/mL sotrovimab administered into the dorsogluteal muscles o 500 mg IM of 100 mg/mL sotrovimab administered into the anterolateral thigh muscles o 500 mg IM of 100 mg/mL sotrovimab administered into the deltoid muscles • Approximately 190 participants will be enrolled to achieve approximately 150 evaluable participants across the four treatment arms. • Visit Frequency: all participants will receive a single dose of sotrovimab on Day 1. 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 will have a phone call visit. Additionally, participants will need to complete a patient-reported outcome (PRO) assessment at home on Day 1. Participants will also need to complete a PRO assessment at the site on Days 2, 3, 5, and 8. Screening assessment will be performed within 28 days prior to dosing, leading to a maximum study duration of 39 weeks. • Follow-up will occur via site and home visits, and a phone call visit at Week 35. **Part C Cohort 1:** • 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. • Cohort 1: Single IV infusion of sotrovimab at 3000 mg dose, infused over 60 minutes (100 mg/mL, diluted as per pharmacy manual). • Initial dosing in Cohort 1 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 `. • Approximately 170 additional participants will then be enrolled into this cohort • Visit frequency: all participants in Part C 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

Overview of Study Design and Key Features	
	site or have a home visit at Weeks 8, 12, 20 and 24. At Week 35, the participants will have a phone call visit. Participants can be screened up to 28 days before dosing; therefore, the maximum duration a participant will be in the study is 39 weeks.
Study Intervention	• Part A: Sotrovimab IM Injection, 62.5 mg/mL or 100 mg/mL will be provided in 1 or 2 single-use vials. • Part C Cohort 1: IV Infusion of sotrovimab 100 mg/mL (diluted as per pharmacy manual) will be provided in 12 single-use vials. • In Part A, approximately o 63 participants will receive 500 mg sotrovimab (62.5 mg/mL) into dorsogluteal muscles on Day 1. o 63 participants will receive 500 mg sotrovimab (100 mg/mL) into dorsogluteal muscles on Day 1. o 32 participants will receive 500 mg sotrovimab (100 mg/mL) into anterolateral thigh muscles on Day 1. o 32 participants will receive 500 mg sotrovimab (100 mg/mL) into deltoid muscles on Day 1. • In Part C Cohort 1: approximately 200 participants will receive IV Infusion of sotrovimab at 3000 mg dose infused over 60 minutes (100 mg/mL, diluted as per pharmacy manual). • Part C enrollment will not be linked to Part A enrollment.
Study Intervention Assignment	• This is an open-label study; however, the specific intervention to be administered to a participant will be assigned using an Interactive Voice/Web Response (IVRS/IWRS). • In Part A, participants will be stratified by sex and two body mass index (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. Sentinel cohorts in each study part are not required to be balanced by sex and BMI strata.
Time & Events	• Refer to Section 6.3 Appendix 2 Schedule of Activities
Interim Analysis	• An interim analysis (IA) for Part A will be performed once approximately half of the participants in Part A complete at least Day 8. • An IA for Part C will be conducted after approximately half of the participants in Part C Cohort 1 complete at least Day 15. Please refer to Section 4.5 for more details.

2. 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.

An estimation approach will be used to describe the pharmacokinetics of sotrovimab. An assessment of relative bioavailability with concentration effect (100 mg/mL IM sotrovimab into dorsogluteal muscles vs. 62.5 mg/mL IM sotrovimab into dorsogluteal muscles), and injection site effect (100 mg/mL IM sotrovimab into anterolateral thigh and deltoid vs. 62.5 mg/mL IM sotrovimab into dorsogluteal muscles) will be conducted for selected pharmacokinetic parameters, where point estimates along with 90% CI will be reported, where appropriate.

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.

2.1. Multiplicity Adjustment

No multiplicity adjustment is planned for this study.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	• Study Population
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.	• Study Population (Part C)
Randomized	All participants who were randomly assigned to study intervention.	• Study Population (Part A)
Safety	All randomized (Part A)/ enrolled (Part C) participants who were exposed to study intervention. Participants will be reported according to the intervention they actually received.	• Safety • Study Population • PRO Assessments • CCI [redacted]
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 • Safety
PK Principal Stratum	All participants in the PK analysis set who would be able to complete the IM/IV dose. Participants will be reported according to the treatment arm they actually received.	• PK • Safety

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

All data will be reported for each study part separately, and separately for each Cohort within Part C. The data will be listed and summarized according to GSK reporting standards, where applicable. In summary tables, results will be presented by treatment arms. The treatment display format is specified in (OPS) Section 4.2.1Study Treatment Display Descriptors.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, endpoints defined in Section 1.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed. Continuous data (except for PK concentration data) will be summarized using n, mean, standard deviation (SD), median, minimum and maximum; for PK concentration data, between-subject CV (%CV_b), 95% CIs, 5th and 95th percentiles will also be reported along with above mentioned summary statistics; categorical variables will be summarized using n and percentage of participants in each category; log_e-transformed serum concentration and PK parameters will be summarized using geometric mean, 95% CI, SD (logs) and the %CV_b based on geometric mean. To assess relative bioavailability, log_e-transformed PK parameters will be statistically analyzed separately using Analysis of covariance (ANCOVA) Model to report point estimate for the ratio of the geometric means of treatment groups under comparison along with 90% CI.

In the case of a difference between the stratification assigned at the time of randomization and the data collected in the electronic case report form (eCRF), the analyses will be performed based on the data collected in the eCRF, not the assigned stratum at randomization.

For all study parts, JSRT will review safety data at regular intervals as described in the JSRT charter. During review of the Part A Sentinel cohort, the JSRT will review the participant data after all of the arms within a study Part have approximately 5 participants who have completed at least Day 8. This will include at least AE, SAE, AESI (including injection site reactions [ISRs]) and safety lab results. In Part A, an interim analysis (IA) will be conducted to review Part A data and decide whether to open Part B and, if needed, the selection treatment arms Part B; In Part C, an IA will be performed to support periodic data reviews across the program. Refer to Section 4.5 for more details.

4.1.2. Baseline and Post-Baseline Definition

For all endpoints (except for electrocardiogram [ECG]) the baseline value will be the latest pre-dose assessment with a non-missing value on or after Day -1 visit, including those from unscheduled visits. For ECG endpoints, which pre-dose measurements are only planned at Screening visit, the baseline value will be the most recent pre-dose assessment with non-missing value before Day 1 visit, including unscheduled visits. If triplicate 12-lead ECGs are collected at the last pre-dose assessment, the average of the

three measurements will be used as baseline record. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If triplicate 12-lead ECGs are collected at any post-baseline visit, the average of the three measurements will be calculated and used in derivation of summary statistics.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Post-Baseline is defined as an occurrence after first dose of the treatment on Day 1.

4.2. Primary Endpoint(s)/Estimands Analyses

4.2.1. Pharmacokinetics

4.2.1.1. Estimands

Table 1 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_{D1-29} 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_{D1-29} 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 in Part A.

4.2.1.2. Definition of Endpoint(s)

Relative bioavailability comparisons (100 mg/mL IM sotrovimab at the dorsogluteal injection site relative to the 62.5 mg/mL formulation administered dorsogluteally) will be performed upon availability of PK data up to Day 29 for Part A.

4.2.1.3. Main Analytical Approach

Relative Bioavailability Assessment
Endpoint(s)
• C_{max}, AUC_{D1-29}
Model Specification
• log_e-transformed value of endpoints will be statistically analyzed separately using analysis of covariance (ANCOVA) with the following terms: ○ **Dependent variable:** C_{max}, AUC_{D1-29} ○ **Covariates:** sex, baseline BMI, treatment (62.5 mg/mL IM sotrovimab into dorsogluteal muscles, 100 mg/mL IM sotrovimab into dorsogluteal muscles, 100 mg/mL IM sotrovimab into anterolateral thigh and 100 mg/mL IM sotrovimab into deltoid) Data will be analyzed for PK Principal Stratum Analysis Set in Part A. • The analysis will be performed using the mixed linear model procedure within the SAS/STAT module of the SAS system. • Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between 100 mg/mL sotrovimab (dorsogluteal muscles) and 62.5 mg/mL sotrovimab (dorsogluteal muscles). The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and their 90% CIs for the ratios, test/reference in PK parameter values on the original scale. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
Model Checking & Diagnostics
• For ANCOVA, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable
Model Results Presentation
• Geometric least-squares means for each treatment arm (100 mg/mL and 62.5 mg/mL IM sotrovimab [dorsogluteal], respectively), point estimates and associated 90% CIs for the ratios for each parameter will be produced in tabular format. • Plots of geometric mean ratio of test to reference treatment arm (100 mg/mL IM sotrovimab vs. 62.5 mg/mL IM sotrovimab [dorsogluteal]) together with 90% CIs will be produced.

4.2.2. Safety

4.2.2.1. Estimands

Table 2 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

4.2.2.2. Definition of Endpoint(s)

The primary safety endpoints for the primary safety objectives (Part A: safety and tolerability of 100 mg/mL and 62.5 mg/mL IM sotrovimab at the dorsogluteal injection sites; Part C: safety and tolerability of IV sotrovimab) are:

- Incidence of AEs through Day 29
- Incidence of SAEs through Day 29
- Incidence of AESIs through Day 29

4.2.2.3. Main Analytical Approach

The analyses described in the following sections, will be performed using the Safety analysis set in all study parts, as defined in Section 3. Unless otherwise specified, available data will be analyzed as collected regardless of intercurrent events that may occur (treatment policy). Missing data will not be imputed.

Incidence of AEs, SAEs, and AESIs through Day 29 will be displayed in the form of summaries and listings, where appropriate. Further details are provided below.

Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary. Adverse events analyses including the analysis of AEs, SAEs and other significant AEs will be based on GSK Core Data Standards.

Adverse event displays to be generated include: overview of AEs, all AEs, all SAEs, AEs leading to permanent discontinuation of study treatment or permanent withdrawal from study, common (≥ 5%) AEs, common (≥ 5%) Non-Serious AEs, common (≥ 5%) SAEs, Drug-related AEs, Serious Drug-related AEs, Non-Serious Drug-related AEs, and Adverse events leading to withdrawal. For Part C, common (≥ 1%) AEs, common (≥ 1%) Non-Serious AEs, common (≥ 1%) SAEs may be additionally reported. The number and percentages of participants with the event will be summarized by System Order Class (SOC) and Preferred Term (PT), unless otherwise specified in the OPS. Adverse Events including fatal SAEs and AEs leading to withdrawal will also be listed as specified in the OPS.

A drug-related AE is defined as an AE for which the investigator classifies the relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing.

Adverse Events of Special Interest

Adverse events of special interest will be monitored by GSK at Day 29 and 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:

- Hypersensitivity reactions occurring any time post dose

- Infusion-related reactions within 24 hours post dose (Part C)
- Injection site reactions (Part A)
- Immunogenicity
- AEs potentially related to antibody-dependent enhancement of disease

AESI of hypersensitivity reactions occurring any time post dose, infusion-related reactions within 24 hours post dose and injection site reactions will be recorded in CRF. For reporting purposes, the MedDRA SMQs or HLTs will be used if applicable or custom list of PTs as agreed with JSRT and aligned with current MedDRA version at the time of reporting. For each of these AESI, the number and percentages of participants with the event will be summarized. Events will be summarized by PT, unless otherwise specified in the OPS. For AESI of injection site reactions (applicable to IM route of administration only), in addition, a cumulative distribution curve of time to first injection site reaction will be produced for each treatment arm.

AEs potentially related to immunogenicity will be reviewed directly from the overall subject anti-drug antibody and AE listings and will be detailed in the CSR. AEs potentially related to antibody-dependent enhancement will be reviewed directly from the COVID-19 infected participants and AE listings and will be detailed in the CSR.

4.3. Secondary Endpoint(s)

4.3.1. Pharmacokinetics

4.3.1.1. Estimands

Table 3 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_{D1-29} and C_{max} through Day 29 • AUC_{inf} through Week 24 • Serum PK of sotrovimab through Day 29 and Week 24
Treatment Conditions	• AUC_{D1-29} 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

Primary Estimand	
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_{D1-29} 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

Table 4 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 C_{max} through Day 29 • Serum PK of sotrovimab through Day 29 and Week 24
Treatment Conditions	• AUC_{D1-29} and C_{max} 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 C_{max} through Day 29: Geometric mean

Primary Estimand	
	• Serum PK of sotrovimab through Day 29 and Week 24: Geometric mean

4.3.1.2. Definition of Endpoint(s)

Serum concentrations will be listed and summarized using descriptive statistics. Positive pre-dose concentrations, post-dose samples below the limit of quantification (BLOQ) will be excluded from summary statistics.

Serum pharmacokinetic parameters will be calculated by standard non-compartmental methods using the currently supported version of WinNonlin (currently version 8.3.1.)

Calculations of pharmacokinetic parameters for the analysis will be based on actual sampling times. Pharmacokinetic parameters listed in Table 5 will be determined from the serum concentration-time data, as data permits. If parameters cannot be determined, a 'Not done' or 'Not calculable' flag will be present in the data.

AUC will be computed using the log down, linear up trapezoidal rule. Where $\%AUC_{exp}$ >20%, AUC_{inf} and all related parameters (i.e., CL/F, Vz/F, variance) will be presented in listings but excluded from the calculation of summary statistics. The decision as to which data points describe the terminal phase will be reached by inspecting the semilogarithmic plot of the data, only considering concentrations at time points beyond T_{max}. A minimum of 3 data points will be used for the estimation of λ_z. For poorly estimated λ_z (i.e., a span of <2 half-lives or $R^2 \leq 0.80$), the corresponding $t_{1/2}$ values will be excluded from summary statistics. C_{max} and T_{max} will be presented in listings but excluded from the calculation of summary statistics if there is insufficient data from the absorption phase (IM) or the end of infusion (IV). Any parameters for which estimates are available in fewer than 3 participants per treatment group will be excluded from descriptive statistics.

PK data from this study may be combined with data from other studies for the purpose of PopPK model development. Details of any future analyses and results will be provided in a separate PopPK analysis plan and report, if applicable.

Table 5 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
$\%AUC_{exp}$	Percentage of AUC_{INF} due to extrapolation from T_{last} to infinity
λ_z	Terminal elimination rate constant
AUC_{D1-29}	Area under the concentration-time curve from study Day 1 to Day 29.
AUC_{last}	Area under the serum concentration-time curve from time zero to time of last measurable (positive) concentration
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
CL (IV) CL/F (IM)	Apparent total clearance
C_{max}	Maximum observed serum concentration, determined directly from the concentration-time data.
C_{last}	The last observed quantifiable serum concentration
T_{max}	Time to reach C_{max}, determined directly from the concentration-time data.
$t_{½}$	Terminal elimination half-life will be calculated as: $t½ = ln2/\lambda z$
T_{last}	Time to reach the last quantifiable concentration
V_z (IV) V_z/F (IM)	Apparent volume of distribution will be calculated as: $Vz/F = \frac{CL/F}{\lambda z}$

NOTES: Additional parameters may be included as required. The parameters to be included in each in OPS.

4.3.1.3. Main Analytical Approach

The secondary pharmacokinetic analyses will be based on the PK analysis set in all study parts, unless otherwise specified. Available data will be analyzed as collected regardless of intercurrent events that may occur (treatment policy). Missing data will not be imputed.

Drug concentration measures

Concentrations of sotrovimab in serum through Day 29 and Week 24 will be listed for all participants by actual time and summarized by treatment arm, concentration and nominal time. Standard summary statistics will be calculated (i.e. n, arithmetic mean, 95% CI, standard deviation, median, minimum, maximum, $\%CV_b$, 5^{th} and 95^{th} percentiles). Refer to the R&D Guideline: Non-Compartmental Analysis of Pharmacokinetic Data, GUI_000722 (v6.0), for more information regarding the treatment of serum concentrations that are BLOQ.

Individual serum concentration-time profiles and median/mean profiles by treatment arm and by concentration will be plotted for each participant within one figure both on the untransformed scale (i.e. a linear plot) and on the log transformed scale (i.e. log-linear plot). See OPS Section 2 List of Data Displays/ TFL Table of Content for details.

Derived Pharmacokinetic Parameters

Parameters will be summarized according to the method defined in Section 4.3.1.1 as described below. Individual participant PK parameter values and a descriptive summary will be reported by treatment arm (for all study parts) and by concentration (for Part A only). Data display specifications for derived PK parameter summaries and listings are provided in OPS Section 2 List of Data Display/ TFL Table of Content.

Table 6 Summary Statistics for Transformed and Untransformed PK Parameters

Untransformed Data: all parameters	n, arithmetic mean, 95% CI for the arithmetic mean, SD, median, minimum, maximum, $\%CV_b$ (percent coefficient of variation between subjects)
Log_e-transformed Data: all parameters except for T_{max}, T_{last}, $t_{½}$, and λ_z	n, geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and $\%CV_b$

The following statistical analyses will also be performed for the following derived PK parameters from evaluable participants. Evaluable participants are defined as those who have sufficient PK concentration data to allow estimation of PK parameters used for secondary endpoint analysis (i.e., AUC_{D1-29} and Cmax).

Part A:

For Part A, the comparisons of relative bioavailability on Day 29 will be conducted for 100 mg/mL IM sotrovimab at 2 alternative injection sites (anterolateral thigh and deltoid) relative to the 62.5 mg/mL formulation administered dorsogluteally.

1. Injection Site Effect on Relative Bioavailability (for Part A Day 29 SAC)
Endpoint(s)
• C_{max}, AUC_{D1-29}
Model Specification
• log_e-transformed values of endpoints will be statistically analyzed separately using ANCOVA with the following terms: ○ **Dependent variable:** C_{max}, AUC_{D1-29} ○ **Covariates:** sex, baseline BMI, treatment (62.5 mg/mL IM sotrovimab into dorsogluteal muscles, 100 mg/mL IM sotrovimab into dorsogluteal muscles,

1. Injection Site Effect on Relative Bioavailability (for Part A Day 29 SAC)
100 mg/mL IM sotrovimab into anterolateral thigh and 100 mg/mL IM sotrovimab into deltoid) Data will be analyzed for PK Principal Stratum Analysis Set in Part A. Point estimates and their associated 90% CI will be constructed for the differences in PK parameter values between the test injection sites (100 mg/mL IM sotrovimab [anterolateral thigh], 100 mg/mL IM sotrovimab [deltoid]) and reference injection site (62.5 mg/mL IM sotrovimab [dorsogluteal muscles]). The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and their 90% CIs for the ratios, test/reference in PK parameter values on the original scale. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
Model Checking & Diagnostics
• For ANCOVA, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable
Model Results Presentation
• Geometric least-squares means for each treatment (100 mg/mL IM sotrovimab into anterolateral thigh, 100 mg/mL IM sotrovimab into deltoid and 62.5 mg/mL IM sotrovimab into dorsogluteal muscles), point estimates and associated 90% CIs for the ratios (100 mg/mL IM sotrovimab [anterolateral thigh]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles], 100 mg/mL IM sotrovimab [deltoid]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles]) for each parameter will be produced in tabular format. • Comparative plots of individual PK parameters will be generated on linear and semi-logarithmic scales. • Plots of geometric mean ratio of test to reference treatment (100 mg/mL IM sotrovimab [anterolateral thigh]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles], 100 mg/mL IM sotrovimab [deltoid]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles]) together with 90% CIs will be produced.

In addition, for Part A, the comparisons of relative bioavailability at Week 24 will also be performed for 100 mg/mL IM sotrovimab at 3 injection sites (dorsogluteal, anterolateral thigh, and deltoid) relative to the 62.5 mg/mL formulation administered dorsogluteally.

2. Injection Site Effect on Relative Bioavailability (for Part A Week 24 SAC)
Endpoint(s)
• AUC_{inf}
Model Specification

2. Injection Site Effect on Relative Bioavailability (for Part A Week 24 SAC)

- log_e-transformed values of endpoints will be statistically analyzed using ANCOVA with the following terms:
    - **Dependent variable:** AUC_{inf}
    - **Covariates:** sex, baseline BMI, treatment (62.5 mg/mL IM sotrovimab into dorsogluteal muscles, 100 mg/mL IM sotrovimab into dorsogluteal muscles, 100 mg/mL IM sotrovimab into anterolateral thigh and 100 mg/mL IM sotrovimab into deltoid)

Data will be analyzed for PK Principal Stratum Analysis Set in Part A.

- Point estimates and their associated 90% CI will be constructed for the differences in PK parameter values between the test treatment (100 mg/mL IM sotrovimab into dorsogluteal muscles, 100 mg/mL IM sotrovimab into anterolateral thigh, 100 mg/mL IM sotrovimab into deltoid) and reference treatment (62.5 mg/mL IM sotrovimab into dorsogluteal muscles). The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and their 90% CIs for the ratios, test/reference in PK parameter values on the original scale.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Model Checking & Diagnostics

- For ANCOVA, model assumptions will be checked, and appropriate adjustments may be applied based on the data.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable

Model Results Presentation

- Geometric least-squares means for each treatment (100 mg/mL IM sotrovimab into anterolateral thigh, 100 mg/mL IM sotrovimab into deltoid, 100 mg/mL IM sotrovimab into dorsogluteal muscles and 62.5 mg/mL IM sotrovimab into dorsogluteal muscles), point estimates and associated 90% CIs for the ratios (100 mg/mL IM sotrovimab [anterolateral thigh]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles], 100 mg/mL IM sotrovimab [deltoid]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles], and 100 mg/mL IM sotrovimab [dorsogluteal muscles]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles]) for each parameter will be produced in tabular format.
- Comparative plots of individual PK parameters will be generated on linear and semi-logarithmic scales.
- Plots of geometric mean ratio of test to reference treatment (100 mg/mL IM sotrovimab [anterolateral thigh]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles], 100 mg/mL IM sotrovimab [deltoid]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles], and 100 mg/mL IM sotrovimab [dorsogluteal muscles]:62.5 mg/mL IM sotrovimab [dorsogluteal muscles]) together with 90% CIs will be produced.

4.3.2. Safety

4.3.2.1. Estimand

Table 7 Primary Estimand for Secondary 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[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 8 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

4.3.2.2. Definition of Endpoint(s)

For Part A, the secondary safety endpoints are:

- Incidence of AEs through Day 29 (100 mg/mL IM sotrovimab administered at anterolateral thigh and deltoid injection sites) and Week 35 (all treatment arms)
- Incidence of SAEs through Day 29 (100 mg/mL IM sotrovimab administered at anterolateral thigh and deltoid injection sites) and Week 35 (all treatment arms)
- Incidence of AESIs through Day 29 (100 mg/mL IM sotrovimab administered at anterolateral thigh and deltoid injection sites) and Week 35 (all treatment arms)

- Incidence of clinically significant changes in vital signs compared to baseline through Day 29 and Week 35
- Incidence of clinically significant laboratory abnormalities through Day 29 and Week 35

For Part C Cohort 1, the secondary safety endpoints are:

- Incidence of AEs through Week 35
- Incidence of SAEs through Week 35
- Incidence of AESIs through Week 35
- Incidence of clinically significant changes in vital signs compared to baseline through Day 29 and Week 35
- Incidence of clinically significant laboratory abnormalities through Day 29 and Week 35

4.3.2.3. Main Analytical Approach

The analyses will be performed using the Safety analysis set in all study parts, as defined in Section 3. Unless otherwise specified, available data will be analyzed as collected regardless of intercurrent events that may occur (treatment policy). Missing data will not be imputed.

Adverse Events, Serious Adverse Events and Adverse Events of Special Interests

Occurrence of AEs, SAEs, and AESIs through Week 35 will be displayed in the form of summaries and listings, where appropriate.

Unless otherwise specified, the secondary safety endpoints will be analyzed as described in Section 4.2.2.2 for the primary safety endpoints.

Vital Signs

Vital sign data include temperature, pulse rate (PR), oxygen saturation (SpO_2), respiratory rate, and blood pressure.

Summary statistics for all results and changes from baseline will be provided in a table by visit for each test. For each test, worst case for each participant will also be summarized by visit. In addition, number of participants with increase in maximum grade from baseline will be summarized by visit for each parameter in a table. A shift table will also be generated to present the shift in post-baseline maximum grade from baseline by visit and overall worst-case post-baseline.

All vital sign data, as well as participants with abnormalities of potential clinical importance and grade will be provided in listings.

Clinical Laboratory Data

Clinical laboratory tests to be performed are listed in Appendix 3. For laboratory tests including hematology, coagulation, clinical chemistry and urinalysis, baseline, post-baseline and change from baseline results will be summarized by treatment arms.

Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range provided by local lab as: “low” (below the lower limit), “normal” (within the normal range) and “high” (above the upper limit). The shift on worst-case post-baseline categories of laboratory result from baseline for each parameter will be summarized by visit in a table.

Laboratory results including hematology, coagulation, clinical chemistry and urinalysis will be graded as Grade 0, 1, 2, 3 or 4 based on Division of AIDS (DAIDS) criteria listed in Appendix 1. The increases on maximum grades will summarized by visit for each parameter. Furthermore, for each parameter of hematology, coagulation and clinical chemistry, the shift of post-baseline maximum grade from baseline will be summarized by visit and overall worst case postbaseline.

SI units will be used for clinical laboratory summary tables and listings. Participants who had shifts from baseline will be listed, along with flags to indicate the abnormalities (“low” and “high”). Laboratory evaluations will be based on GSK Core Data Standards. The details of the planned displays are provided in the OPS Section 2, List of Data Displays/ TFL Table of Content.

Electrocardiograms

ECG data will include heart rate, PR, QRS, QT, and corrected QT (QTc). The QTc data analysis will use the collected values based on Fridericia formula.

ECG findings are defined from best to worst as: “normal”, “abnormal - not clinically significant”, and “abnormal - clinically significant”. The worst finding will be selected at each time point when there is repeat ECG. All ECG findings will be summarized for screening visit. In addition, the QTcF values will be summarized in a table by categories of “≤ 450 msec”, “451-480 msec”, “481-500 msec”, “≥ 501 msec”, and “missing”. Worst -case post baseline of QTcF values is calculated as the maximum assessment of each “QTcF Interval, Aggregate (msec)”.

A listing of ECG values for participants with abnormalities of potential clinical importance will be provided. In addition, clinically significant ECG findings will be listed in a separate listing.

Extent of Exposure

Listings of data on participant exposure will be generated for each treatment arm.

4.4. Tertiary/Exploratory Endpoint(s)

4.4.1. Immunogenicity and Virologic Assessments

4.4.1.1. Definition of Endpoint(s)

Antibodies to sotrovimab will be evaluated in serum samples collected from all participants according to the SoA (Appendix 2). Additionally, serum samples should also

be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

CCI [redacted]

SARS-CoV-2 will be tested for all participants at screening and on Day -1. CCI [redacted]

CCI [redacted].

4.4.1.2. Main Analytical Approach

The analyses will be performed using the Safety analysis set in all study parts, as defined in Section 3. Unless otherwise specified, available data will be analyzed as collected regardless of intercurrent events that may occur (treatment policy). Missing data will not be imputed.

Incidence of serum anti-drug antibody (ADA), drug-neutralizing antibodies to sotrovimab and titers will be summarized by visit for each treatment arm. CCI [redacted]. In addition, all immunogenicity and virologic data will be listed.

4.4.2. Patient-reported Outcomes (PRO) (Part A)

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).

In addition, 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).

4.4.2.1. Definition of Endpoint(s)

The exploratory endpoints of PRO include

- 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.
- 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.

4.4.2.2. Main Analytical Approach

The analyses will be performed using the Safety analysis set in Part A, as defined in Section 3.

Incidence of each answer to the questions on PIN questionnaire will be summarized (i.e., Not at all, A little, Moderately, Very, Extremely, No answer provided) in a table for each treatment arm. The intensity ratings collected on pain-NRS will also be summarized in a separate table.

Listings of PIN_TS3.0 and pain-NRS results will also be generated.

4.4.3. Local Injection Site Tolerability Assessment (Part A)

Local injection site tolerability assessment will be performed on Day 1 (at approximately 15 minutes, 30 minutes, and 1hour post-dose) and on Days 2, 3, 5, and 8.

The grade of local tolerability assessment will be summarized in tables for each treatment arm based on Safety analysis set in Part A. The assessment results will also be listed for all participants in Safety analysis set in Part A.

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

4.6. Interim Analyses

A JSRT will review safety data for all study parts at regular intervals as described in the JSRT charter. Data will be reviewed directly from the EDC tool. In Part A, a planned sentinel review will be conducted after approximately 5 participants per arm complete at least Day 8 visit as described in Protocol Amendment 2 (dated 06-Sep-22; TMF-15739935) Section 4.1. The details of possible of decisions to be made by JSRT is included in Protocol Amendment 2 Section 4.1 Overall Design. In Part C, an in-stream safety lead-in data review will occur after approximately 30 participants have completed at least Day 8 as described in Protocol Amendment 2.

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.

Part A:

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. The database will be cleaned and database freeze will be declared by Data Management. The randomization will then be unblinded in order to conduct the IA. The

outputs to be used for IA are specified in the OPS Section 2.7, which include demographic and baseline disease characteristics, and safety reports. Any available PK data up to Day 29 at the time of the IA may be included. Recruitment into Part A will continue with no pause at the time of the interim analysis. Thereafter, participants will continue to complete the remaining schedule of assessments as per the protocol.

Part C:

An IA will be conducted after approximately half of the participants in Cohort 1 complete at least Day 15 visit, to support periodic data reviews across the programme. The data will be cleaned per data management plan (DMP), and database freeze will be declared by Data Management team. All available data in the database at the time of the data cut date will be reported in the outputs, regardless of the level of cleaning per the DMP.

The outputs to be used for IA are specified in the OPS Section 2.8. Any available PK data up to Day 29 at the time of the IA may be included.

4.7. Planned Analyses

The planned analyses for each study part will be performed separately, and separately for each Cohort within Part C.

After approximately half of the participants in Part A complete at least Day 8 visit, the data will be formally unblinded and the analyses planned in OPS Section 2.5 will be conducted. This will be considered as Part A IA SAC.

After approximately half of the participants in Part C Cohort 1 complete at least Day 15 visit, the data will be formally unblinded and the analyses planned in OPS Section 2.8 will be conducted. This will be considered as Part C Cohort 1 IA SAC.

Once the last participant is recruited and completes assessments through Day 29 within their respective study part and Cohort (Part A or Part C Cohort 1), the data specified in DMP will be cleaned and formally unblinded in the systems to allow a readout of the Day 29 endpoints. These will be considered as the Part A Day 29 SAC and Part C Cohort 1 Day 29 SAC respectively.

Part A and Part C Cohort 1 participants will continue to complete the remaining scheduled assessments up to Week 35. Once all participants complete Week 24 assessments, a Week 24 SAC will be conducted to allow a readout of all safety and PK endpoints through Week 24. The final planned analyses will be performed after all participants have completed Week 35 assessments. These will be considered as the final Part A Week 35 SAC and final Part C Cohort 1 Week 35 SAC. See Section 4.2, Section 4.3, and Section 4.4 for all planned analyses for this study.

Any changes/ deviations to the analyses specified in the SAP will be described in the CSR.

Displays will be produced according to Clinical data interchange standards consortium (CDISC) reporting standards based on the final Study data tabulation model (SDTM) and Analysis data model (ADAM) datasets.

4.8. Changes to Protocol Defined Analyses

There are no changes from the originally planned statistical analysis described in the protocol.

5. SAMPLE SIZE DETERMINATION

The planned sample sizes for the number of evaluable participants in each treatment arm in Part A 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 two 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 anterolateral thigh and deltoid arms in Part A. Therefore, the total number of evaluable participants planned in this study is **150 in Part A**. To account for an expected 20% rate of non-evaluable participants approximately 190 participants will be randomized into Part A.

Sample size determinations are based on an assumed between participant CV_b for AUC_{D1-29}, 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_{D1-29} 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.
With an IA consisting of 100 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 2.28 %.
The precision of event rate estimation is shown in the table below, as indicated by the width of 95% confidence intervals.

Precision of Estimated Event Rate:

Total Number of Participants	**Observed Event Rate**	**Number of Participants with a Particular Event Observed**	**95% Confidence Interval**
100 (individual study size for Part C Cohort 1 IA)	0.5%	1	(0.03%, 5.45%)
	1.0%	1	(0.03%, 5.45%)
	2.0%	2	(0.24%, 7.04%)
	5.0%	5	(1.64%, 11.28%)
	10.0%	10	(4.90%, 17.62%)
	50.0%	50	(39.83%, 60.17%)
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%)

6. SUPPORTING DOCUMENTATION

6.1. Study Population Analyses

The precise format and content of Study Population tables and listings are shown in OPS Section 2 List of Data Displays/ TFL Table of Content.

The summaries/listings will use the Safety analysis set in all study parts unless otherwise specified.

6.1.1. Participant Disposition

Study status for all original participants including ongoing, completed, and withdrawn, as well as primary reason for study withdrawal and outcome of adverse events leading to study withdrawal will be summarized. The status of a participant is considered completed when he/she has completed the Week 35 visit. If a participant withdraws early from the study after week 24, the status will be considered as early withdrawal. A separate table for study status will also be produced by relation to the COVID-19 pandemic.

A summary table of the number of participants who passed screening and entered the study or failed screening and therefore did not enter the study, will also be provided along with reason for screen failure. This will be performed on the Screened analysis set. Participants who failed screening and the reason for screen failure will be listed.

The number of participants in each analysis set (Screened, Randomized, Safety, PK and PK Principal Stratum) will be summarized by treatment arm in a table. This table will be based on the Screened analysis set in all study parts. A listing of participants excluded from any analysis set will also be provided for the Screened analysis set in all study parts.

A summary table will be generated providing the count of participants in each treatment arm at each site included for randomized, safety, PK and PK principal stratum analysis sets respectively (see Section 3 for definition of analysis sets).

Listings of participants who discontinued the study will be generated.

6.1.2. Demographic and Baseline Characteristics

Demographic data include year of birth, sex at birth, race, ethnicity, height in centimeters, body weight in kilogram (kg), BMI in kg/m^2 and BMI category. Demographic data will be summarized and listed for the Safety analysis set. The duration of participants on study post-dose will be summarized in a table for the Safety analysis set. The local SARS-CoV-2 test results and risk factors for COVID-19 will be summarized in a baseline disease characteristics table for all treatment arms. Age ranges will be summarized in a separate table for the Randomized analysis set. The race and race combination details of participant will also be summarized in a table by treatment arms.

In addition, the past and current medical conditions will be summarized by treatment arm in two separate tables. Gender Identity data is being collected as part of a pilot in Part C. This data will be reported as a part of the demographic listings.

A listing of actual and randomized strata will also be generated.

6.1.3. Protocol Deviations

Documented important protocol deviations will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Participants who did not satisfy all inclusion and exclusion criteria and corresponding criteria that were violated will be listed.

6.1.4. Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug coding dictionaries. However, they will only be summarized using the GSK Drug dictionary. Concomitant medications will be summarized by the Anatomical Therapeutic Chemical Classification level 1 (ATC Level 1) and by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Concomitant medications will also be listed.

6.1.5. Substance Use

Substance use of tobacco, alcohol and caffeine and will be collected in the eCRF. A summary table will be generated for substance use including tobacco history, alcohol history, number of units of alcohol/week, caffeine history, number of units of caffeine/week. All substance use data will also be displayed in a listing.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

To assess the impact of the COVID-19 pandemic, additional analyses will be produced. A summary of the number and percentage of participants with visits impacted by the COVID-19 pandemic will be produced.

CCI [redacted].

See also Section 6.1.1, for additional disposition table in relationship to the COVID-19 pandemic.

6.2. Appendix 1 Data Derivations Rule

6.2.1. Change from Baseline

The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

6.2.2. Pharmacokinetic Parameters

For the purposes of calculating summary statistics and for statistical analysis, all PK parameters with the exception of T_{max}, T_{last}, $t_{1/2}$ and λ_z will be $\log_e$ transformed.

Between subject coefficient of variation $\%CV_b$ will be calculated according to the following methods:

Untransformed Data : $\frac{SD}{mean} \times 100$,

Transformed Data : $\sqrt{e^{SD^2} - 1} \times 100$,

where SD^2 = variance of $\log_e$ transformed data.

6.2.3. DAIDS Criteria for Laboratory Result Toxicity Grading

Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Event (DAIDS v2.1) will be used to assign grades to the relevant laboratory parameters.

Clinical Chemistry					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Albumin, Low (g/dL; *g/L*)	> 3.0 > *30*	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 ≥ *20 to < 30*	< 2.0 < *20*	NA
Alkaline Phosphatase, High	< 1.25 x ULN	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT or SGPT, High	< 1.25 x ULN	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x UL
AST or SGOT, High	< 1.25 x ULN	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bilirubin ***Direct Bilirubin, High***	NA	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Bilirubin	< 1.1 x ULN	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

Clinical Chemistry					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Total Bilirubin, High					
Calcium, High (mg/dL; *mmol/L*)	< 10.6 <*2.65*	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	≥ 13.5 ≥ *3.38*
Calcium, Low (mg/dL; *mmol/L*)	≥ 8.4 ≥ *2.10*	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 < *1.53*
Creatinine, High	< 1.1 x ULN	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	< 110 < *6.11*	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to* < *13.89*	> 250 to 500 *13.89 to* < *27.75*	≥ 500 ≥ *27.75*
Glucose (mg/dL; *mmol/L*) ***Nonfasting, High***	< 116 < *6.44*	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to* < *13.89*	> 250 to 500 *13.89 to* < *27.75*	≥ 500 ≥ *27.75*
Glucose, Low (mg/dL; *mmol/L*)	> 64 > *3.55*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to* < *3.05*	30 to < 40 *1.67 to* < *2.22*	< 30 < *1.67*
Magnesium, Low (mEq/L; *mmol/L*)	≥ 1.4 ≥ *0.70*	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to* < *0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 < *0.30*
Phosphate, Low (mg/dL; *mmol/L*)	> 2.0 >*0.65*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to* < *0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 < *0.32*
Potassium, High (mEq/L; *mmol/L*)	< 5.6 < *5.6*	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 ≥ *7.0*
Potassium, Low (mEq/L; *mmol/L*)	≥ 3.4 ≥ *3.4*	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 < *2.0*
Sodium, High (mEq/L; *mmol/L*)	< 146 < *146*	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 ≥ *160*
Sodium, Low (mEq/L; *mmol/L*)	≥ 135 ≥ *135*	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 ≤ *120*

Hematology					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)	≥ 650 ≥ *0.650 x 10^9*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)	≥ 1,000 ≥ *1.000 x 10^9*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
Hemoglobin, Low (g/dL; *mmol/L*) *(male only)*	≥ 10.9 ≥ *6.76*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
Hemoglobin, Low (g/dL; *mmol/L*) *(female only)*	≥ 10.4 ≥ *6.48*	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
INR, High (not on anticoagulation therapy)	< 1.1 x ULN	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
PTT, High (not on anticoagulation therapy)	< 1.1 x ULN	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	≥ 125,000 ≥ *125,000* *125.000 x 10^9*	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
WBC, Decreased (cells/mm^3; *cells/L*)	≥ 2,499 ≥ *2.499 x 10^9*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*

Urinalysis					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Glucose, Increased Glycosuria	0	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Protein, Increased Proteinuria	0 or trace	1+	2+	3+ or higher	NA

To determine the potential clinical importance, reference ranges for all laboratory parameters collected throughout the study are provided by local laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

6.2.4. Study Day and Reference Dates

The safety and PK reference date is the study intervention start date and will be used to calculate study day for safety and PK measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.5. Multiple measurements at One Analysis Time Point

During screening and during post-baseline visits, triplicate ECG assessments may be taken. Mean of the measurement will be calculated first and recorded. Summary statistics will be based on the recorded mean. This will apply to both baseline and post baseline assessments.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.2.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
o If year of start date = year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>

Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:

</td></tr>
</table>

Element	Reporting Detail	
	Missing start day	If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: o If month and year of start date = month and year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. ▪ Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: o If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. ▪ Else set start date = study intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

6.3. Appendix 2 Schedule of Activities (SoA)

Part A

	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
	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
	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]												
	Randomization			X											
	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]							
Assessments	12-lead ECG	X[6]													
Assessments	PIN_TS3.0[7]			X	X	X	X	X							
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	
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[11]	X	X												
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	
Sample collection	Blood sample for immunogenicity testing (ADA and drug-neutralizing antibody)			X[14]						X		X	X	X	
Sample collection	CCI [redacted]			X[14]											
Sample collection	[redacted]			X[14]											

Notes[16]

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 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.
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.
6. Triplicate 12-lead ECGs will be collected at Screening.
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.
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.
9. Baseline laboratory assessments should be collected on Day -1.
10. Hematology assessments will be performed only on Days -1, 2, 5, 8, and 29.
11. Screening and Day -1 tests must be >24 hours apart.
12. Urine or serum pregnancy test, as per local guidelines. See Protocol Amendment.1 (TMF-15739935) Section 8.3.5.
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.

			W1	W2	W3	W4	W8	W12	W20	W24	W35	
AE 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.
SAE review	X[15]	X[15]	<========== X ==========>									
AESI and concomitant medication review			<========== X ==========>									

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; d = day; GSK = GlaxoSmithKline; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EW = early withdrawal; HIV = human immunodeficiency virus; ISRs = injection site reactions; Pain-NRS =injection site pain numeric rating scale; PI = principal investigator; PIN_TS3.0 = perception of injection version 3; 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 Competent Authority (CA) and ethics committee (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 informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

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.
9. Urine or serum pregnancy test, as per local guidelines. See protocol 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.

6.4. Appendix 3 Clinical Laboratory Tests

The tests detailed in Table 12 will be performed by the central or local laboratory.

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

Table 12 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 (BUN)	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 ○ Specific gravity ○ pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick ○ Microscopic examination (if blood, protein is abnormal) • Urine creatinine and urine albumin			
Pregnancy testing	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential [WOCBP])[3]			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone (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 Protocol Amendment.1 (TMF-15739935) Section 7.1 Protocol Amendment.1 (TMF-15739935) 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.

6.5. Appendix 4 Abbreviations

Abbreviation	Description
Ab	Antibody
ADA	Anti-drug antibody
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUC_{D1-29}	AUC from study Day 1 to Day 29
AUC_{last}	Area under the serum concentration-time curve from time zero to time of last measurable concentration
AUC_{inf}	AUC extrapolated to infinity
BLOQ	Below the limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
CA	Competent authority
CDISC	Clinical data interchange standards consortium
CI	Confidence interval
CPMS	Clinical pharmacology modelling & simulation
CSR	Clinical study report
CV_b	Coefficient of variation (between)
CL/F	Apparent clearance
C_{max}	Maximum observed concentration
CRF	Case record form
DAIDS	Division of AIDS
DCO	Data cut-off
EC	Ethnicity committee
ECG	Electrocardiogram
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IA	Interim analysis
INR	International normalized ratio
IRB	Institutional review board
ISR	Injection site reaction
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	Kilogram
OPS	Output and programming specification
PK	Pharmacokinetic

Abbreviation	Description
QTcF	Frederica's QT interval corrected for heart rate
RBC	Red blood cells
SAC	Statistical analysis complete
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	Standard deviation
SDTM	Study data tabulation model
SGOT	Serum Glutamic-Oxaloacetic transaminase
SGPT	Serum Glutamic-Pyruvic transaminase
SMQ	Standardized MedDRA Query
SoA	Schedule of activities
SOC	System order class
SpO_2	Oxygen saturation
PT	Preferred term
aPTT	Activated partial thromboplastin time
TFL	Tables, Figures & Listings
T_{max}	Time taken to maximum observed plasma drug concentration
$t_{1/2}$	Terminal phase half-life
T_{last}	Time of last quantifiable concentration
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution
Vir	Vir Biotechnology, Inc.
VOC(s)	Variants of concern
VOI(s)	Variants of interest
WBC	White blood cells
λ_z	Terminal phase rate constant

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7. REFERENCES

Output and Programming Specifications (OPS) Amendment, Study Number: 218128 (VIR-7831-5012 COSMIC), Compound Number: Sotrovimab (also known as GSK4182136, VIR-7831)

Protocol amendment 3 GlaxoSmithKline Document Number TMF-15739935: 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, 30Mar2023