Statistical Analysis Plan

Study ID: 217653

Official Title of Study: A Phase I, single-blind, randomized, single-dose clinical pharmacology study to investigate the pharmacokinetics, safety, and tolerability of sotrovimab vs placebo by intravenous or intramuscular administration in healthy Japanese and Caucasian participants.

IND Identifier: 149315

Date of Document: 09-AUG-2021

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase I, single-blind, randomized, single-dose clinical pharmacology study to investigate the pharmacokinetics, safety, and tolerability of sotrovimab vs placebo by intravenous or intramuscular administration in healthy Japanese and Caucasian participants
Study Number:	217653 (VIR-7831-5009)
Compound Number:	Sotrovimab (also known as GSK4182136, VIR-7831)
Abbreviated Title:	A Phase I single-dose study to investigate the pharmacokinetics, safety, and tolerability of sotrovimab vs placebo by intravenous or intramuscular administration in healthy Japanese and Caucasian participants

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)

Registry	**ID**
IND	149315

TABLE OF CONTENTS

PAGE

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	09-AUG-2021	Version 1.0 (27May2021)	Not Applicable	Original version

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 217653.

This SAP covers the analyses planned for the following Statistical Analysis Complete (SAC) deliverables: Part 1 Day 29, Part 2 Day 29 and final Week 18 analysis. At the time of writing this SAP, a separate Day 29 Part 2 SAC has not been confirmed. This SAP and the study Output and Programming Specifications (OPS) will include planned analyses for this deliverable, which will be conditional on if a Part 2 Day 29 SAC is agreed. 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 GSK Data Display Standards terminology.

1.1. Objectives, Estimands and Endpoints

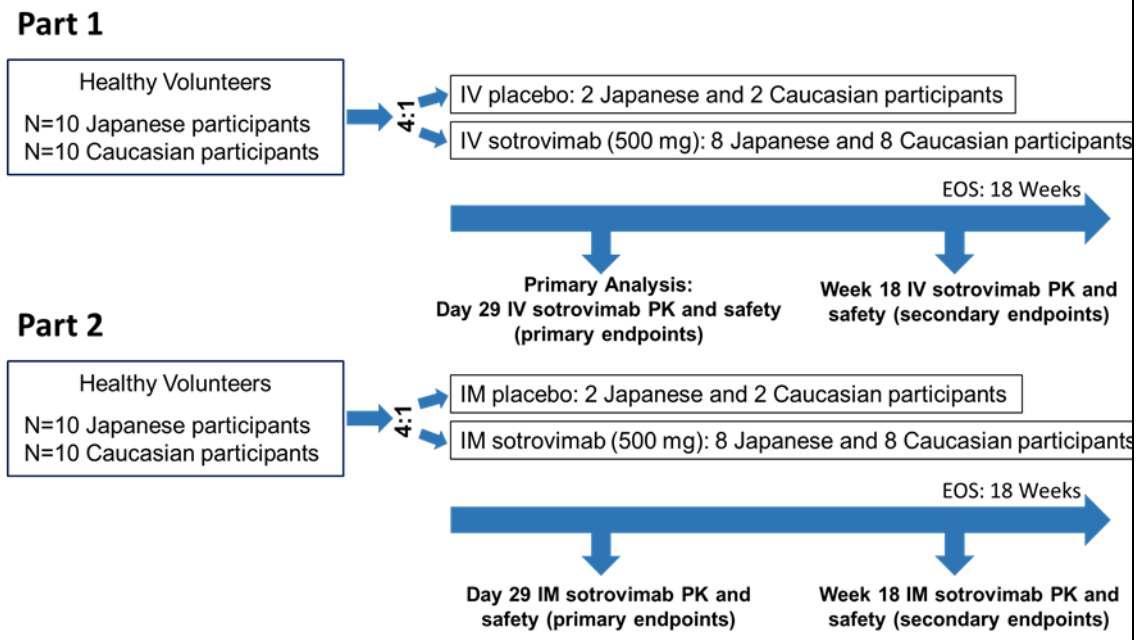
Objectives	Endpoints
Primary	
Pharmacokinetics (Part 1) To assess the pharmacokinetics (PK) of sotrovimab administered via intravenous (IV) infusion in healthy Japanese and Caucasian participants through Day 29	PK parameters through Day 29: maximum observed serum concentration (C_{max}), area under the serum-concentration time curve from Day 1 to Day 29 (AUC_{D1-29}), time to C_{max} (T_{max}), and concentration at Day 29 (C_{D29}) of sotrovimab, as data permits.
Pharmacokinetics (Part 2) To assess the PK of sotrovimab administered via intramuscular (IM) injections in healthy Japanese and Caucasian participants through Day 29	PK parameters through Day 29: C_{max}, AUC_{D1-29}, T_{max}, and C_{D29} of sotrovimab, as data permits.
Safety (Part 1) To evaluate the safety and tolerability profile of IV sotrovimab in healthy Japanese and Caucasian participants through Day 29	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29 • Occurrence of adverse events of special interest (AESIs) through Day 29 • Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29

Objectives	Endpoints
	• Occurrence of clinically significant changes in vital signs compared to baseline through Day 29 • Occurrence of clinically significant laboratory abnormalities through Day 29
Safety (Part 2) To evaluate the safety and tolerability profile of IM sotrovimab in healthy Japanese and Caucasian participants through Day 29	• Occurrence of AEs through Day 29 • Occurrence of SAEs through Day 29 • Occurrence of AESIs through Day 29 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Day 29 • Occurrence of clinically significant changes in vital signs compared to baseline through Day 29 • Occurrence of clinically significant laboratory abnormalities through Day 29
Secondary	
Pharmacokinetics (Part 1) To assess the PK of sotrovimab administered via IV infusion in healthy Japanese and Caucasian participants through Week 18	PK parameters through Week 18: C_{max}, area under the serum concentration-time curve extrapolated to infinite time (AUC_{inf}), area under the curve from the time of dosing to the time of the last measurable (positive) concentration (AUC_{last}), T_{max}, time of the last quantifiable concentration (T_{last}), and the terminal elimination half-life ($t_{1/2}$) of sotrovimab, as data permits.
Pharmacokinetics (Part 2) To assess the PK of sotrovimab administered via IM injections in healthy Japanese and Caucasian participants through Week 18	PK parameters through Week 18: C_{max}, AUC_{inf}, AUC_{last}, T_{max}, T_{last}, and $t_{1/2}$, of sotrovimab, as data permits.

Objectives	Endpoints
Safety (Part 1) To evaluate the safety and tolerability profile of IV sotrovimab in healthy Japanese and Caucasian participants through Week 18	• Occurrence of AEs through Week 18 • Occurrence of SAEs through Week 18 • Occurrence of AESIs through Week 18 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 18 • Occurrence of clinically significant changes in vital signs compared to baseline through Week 18 • Occurrence of clinically significant laboratory abnormalities through Week 18
Safety (Part 2) To evaluate the safety and tolerability profile of IM sotrovimab in healthy Japanese and Caucasian participants through Week 18	• Occurrence of AEs through Week 18 • Occurrence of SAEs through Week 18 • Occurrence of AESIs through Week 18 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 18 • Occurrence of clinically significant changes in vital signs compared to baseline through Week 18 • Occurrence of clinically significant laboratory abnormalities through Week 18
Exploratory	
Immunogenicity (Part 1) To assess the immunogenicity of IV sotrovimab in healthy Japanese and Caucasian participants	Incidence and titers (if applicable) of serum anti-drug antibodies (ADA) and drug-neutralizing antibodies to sotrovimab through Week 18.
Immunogenicity (Part 2) To assess the immunogenicity of IM sotrovimab in healthy Japanese and Caucasian participants	Incidence and titers (if applicable) of serum ADA and drug-neutralizing antibodies to sotrovimab through Week 18.

1.2. Study Design

Overview of Study Design and Key Features



Design Features

- This study is a randomized, multi-center, placebo-controlled, single-blind, single-dose, parallel group Phase I trial to assess the PK of IV and IM sotrovimab in healthy Japanese and Caucasian participants. This study will occur in two parts (Part 1 and Part 2).
- Part 1:
  Healthy Japanese and Caucasian participants will be randomized in a 4:1 ratio to receive a single, 500 mg intravenous infusion of sotrovimab or volume-matched saline placebo. Eligible participants will be treated with a single IV dose of sotrovimab or volume-matched saline placebo on Day 1. Participants will be blinded to study intervention. Safety, tolerability, immunogenicity, and PK of IV sotrovimab will be evaluated.
- Part 2:
  Part 2 will begin after enrollment has been completed for Part 1. Healthy Japanese and Caucasian participants will be randomized in a 4:1 ratio to receive a single, 500 mg IM dose of sotrovimab or volume-matched saline placebo. Eligible participants will be treated with a single IM dose of sotrovimab or volume-matched saline placebo (given as two 4 mL injections, one in each dorsogluteal muscle) on Day 1. Participants will be blinded to study intervention. Safety, tolerability, immunogenicity, and PK of IM sotrovimab will be evaluated.
- Study Duration: 18 weeks after dosing. Participants can be screened up to 28 days before dosing, leading to a maximum study duration of 22 weeks.
- Visit Frequency: Participants will be admitted to the clinical research unit on the day prior to study drug administration (Day -1) and will remain in the unit until all Day 3 study activities are completed. Participants will need to return to the study site for 7 follow-up visits during the 18-week study (at Weeks 2, 3, 4, 6, 8, 12, and 18).

Overview of Study Design and Key Features	
Dosing	• In Part 1, a single dose of sotrovimab 500 mg or placebo, administered IV on Day 1. In Part 2, a single dose of sotrovimab 500 mg or placebo, administered IM on Day 1.
Time & Events	• Refer to Section 6.3 Appendix 2 Schedule of Activities
Treatment Assignment	• Part 1: Participants will be randomised in a 4:1 ratio to receive either IV sotrovimab 500 mg or IV placebo. A maximum of 24 participants will be randomized to Part 1, such that approximately 20 evaluable participants are recruited. The Part 1 cohort will enroll approximately 8 Japanese and 8 Caucasian participants to the IV sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm. • Part 2: Participants will be randomised in a 4:1 ratio to receive either IM sotrovimab 500 mg or IM placebo. A maximum of 24 participants will be randomized to Part 2, such that approximately 20 evaluable participants are recruited in Part 2. The Part 2 cohort will enroll approximately 8 Japanese and 8 Caucasian participants to the IM sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm. • All participants will be centrally randomized using an Interactive Web Response System (IWRS).
Interim Analysis	• No interim analyses are planned.

2. STATISTICAL HYPOTHESES

The primary objectives are to assess the pharmacokinetics, safety, and tolerability of single-dose sotrovimab administered via IV infusion (Part 1) or IM injection (Part 2) in healthy Japanese and Caucasian participants. There are no formal statistical hypotheses planned.

An estimation approach will be used to describe the pharmacokinetics of Sotrovimab. An assessment of the ethnicity effect (Japanese, Caucasian) and absolute bioavailability (IM vs. IV) will be conducted for selected pharmacokinetic parameters, where point estimates along with 90% confidence intervals will be reported, where appropriate.

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: screen failures are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomised	All participants who were randomly assigned to study intervention. Data will be reported according to the randomized intervention.	Study Population
Safety	All randomized participants who were exposed to study intervention. Participants will be reported according to the intervention they actually received.	Safety, Study Population, and Immunogenicity
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment – i.e., PK sample collected and analysed. Note: Non-quantifiable [NQ] values will be considered as non-missing values when defining PK population. Participants will be reported according to the intervention they actually received.	PK and Safety

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who prematurely withdrew from study before Day 29 will be replaced, at the discretion of the Sponsor or designee, in consultation with the investigator.

Parts 1 and 2 will be reported separately, with separate outputs generated for each, unless otherwise stated. In summary tables, results will be presented by treatment arms for each study part and combined treatment arms where applicable. The treatment display format is specified in OPS Section 4.3.1 Study 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 will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum, and geometric mean, 90% confidence interval (CI) and the between-subject CV (%CV_b) based on the geometric mean for the $\log_e$-transformed

PK parameters. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline and Post-Baseline Definition

For all endpoints 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. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For electrocardiogram, 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.

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) Analyses

4.2.1. Pharmacokinetics

4.2.1.1. Definition of Endpoint(s)

Serum pharmacokinetic parameters will be calculated by standard non-compartmental methods according to current Clinical Pharmacology Modelling & Simulation (CPMS) working practices and using the currently supported version of WinNonlin (Currently version 8.0.)

Calculations of pharmacokinetic parameters for the analysis will be based on actual sampling times. Pharmacokinetic parameters listed in Table 1 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.

Table 1 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
$\%AUC_{exp}$	Area under the concentration-time curve extrapolated from time t to infinity as a percentage of total AUC
λ_z	Terminal rate constant
AUC_{D1-29}	Area under the concentration-time curve from Day 1 predose to Day 29.
C_{D29}	Observed Serum concentration on Day 29
CL	Apparent total body clearance of the drug from serum
C_{max}	Maximum observed serum concentration, determined directly from the concentration-time data.

Parameter	Parameter Description
T_{max}	Time to reach $C_{max,}$ determined directly from the concentration-time data.
$t_{½}$	Apparent terminal phase half-life will be calculated as: $t_{½} = \ln 2 / \lambda_z$
T_{last}	Time to reach the last quantifiable concentration (C_t)
V_{ss}	Apparent volume of distribution at steady state
V_z	Apparent volume of distribution during terminal phase

NOTES: Additional parameters may be included as required.

4.2.1.2. Main analytical approach

The primary pharmacokinetic analyses will be based on the PK analysis set, 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.

4.2.1.2.1. Drug concentration measures

Concentrations of sotrovimab in serum through Day 29 will be listed for all participants by actual time and summarised by ethnicity and nominal time. Standard summary statistics will be calculated (i.e. n, geographic mean, arithmetic mean, standard deviation, median, minimum and maximum). 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 below the assay's lower limit of quantification (BLOQ).

Individual serum concentration-time profiles and median/mean profiles by ethnicity and overall 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 Output and Programming Specifications (OPS) Section 2 List of Data Displays/ TFL Table of Content for details.

4.2.1.2.2. Derived PK parameters

Parameters will be summarised according to the method defined in Section 4.2.1.1 as described below. Individual participant PK parameter values and a descriptive summary will be reported by ethnicity. Data display specifications for derived PK parameter summaries and listings are provided in OPS Section 2 List of Data Display/ TFL Table of Content.

Untransformed Data: T_{max}, T_{last}, $t_{½,}$, λ_z	n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum

Log_e-transformed Data: $\%AUC_{exp}$, AUC_{D1-29}, C_{D29}, C_{max}, V_z, V_{ss}, CL	n, geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and $\%CV_b$ (percent coefficient of variation between groups)

The following statistical analyses will also be performed for derived PK parameters only if PK concentration levels exceed the lower level of Quantification (LLQ) for the data to be available.

Pharmacokinetic analysis will be the responsibility of the CPMS and statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

Ethnicity comparisons will be performed on Day 29 for both Part 1 (IV) and Part 2 (IM). For Part 1, this will be done at the planned Day 29 Part 1 SAC and for Part 2 at the Day 29 Part 2 SAC (if applicable). If a separate SAC for Part 2 is not performed, the ethnicity comparison for Day 29 Part 2 will be performed at the final Week 18 SAC instead. Absolute bioavailability comparison will also be conducted on Day 29 after IM data are available.

1. Ethnicity Comparison

Endpoint(s)

- C_{max}, AUC_{D1-29}

Model Specification

- log_e-transformed values of endpoints will be statistically analyzed separately using analysis of covariance (ANCOVA) with the following terms:
    - **Dependent variable:** C_{max}, AUC_{D1-29}
    - **Covariates:** weight, ethnicity (Japanese, Caucasian)

  The analysis will be performed using the mixed linear model procedure within the SAS/STAT module of the SAS system. In Part 1 Day 29 SAC, data will be analyzed for all participants in Part 1 (IV). Under the condition where Part 2 Day 29 SAC is confirmed, the same analysis will be conducted on all participants in Part 2 (IM).
- Point estimates and their associated 90% confidence intervals (CI) will be constructed for the differences in PK parameter values between Japanese and Caucasian. The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and their 90% CIs for the ratios, Japanese/Caucasian 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 ethnicity group (Japanese, Caucasian), point estimates and associated 90% confidence intervals for the ratios for each parameter will be produced in tabular format.
- Plots of adjusted geometric mean ratio of test to reference ethnicity group (Japanese:Caucasian) together with 90% confidence intervals will be produced.

2. Absolute Bioavailability Assessment

Endpoint(s)

- AUC_{D1-29}

Model Specification

- log_e-transformed values of endpoints will be statistically analyzed separately using ANCOVA with the following terms:
    - **Dependent variable:** AUC_{D1-29}
    - **Covariates:** weight, ethnicity (Japanese, Caucasian), route of administration (IV, IM)

  Data will be analyzed for all participants in Part 1 (IV) and Part 2 (IM).
- Point estimates and their associated 90% confidence intervals (CI) will be constructed for the differences in PK parameter values between the test (IM) and reference (IV) treatments. 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 administration route (IV, IM), point estimates and associated 90% confidence intervals for the ratios 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 adjusted geometric mean ratio of test to reference administration route (IM:IV) together with 90% confidence intervals will be produced.

4.2.2. Safety

4.2.2.1. Definition of Endpoint(s)

For Part 1 and Part 2, the primary safety endpoints are:

- Occurrence of AEs through Day 29
- Occurrence of SAEs through Day 29
- Occurrence of AESIs through Day 29
- Occurrence of clinically significant abnormalities on 12-lead ECG reading through Day 29
- Occurrence of clinically significant changes in vital signs compared to baseline through Day 29
- Occurrence of clinically significant laboratory abnormalities through Day 29

4.2.2.2. Main analytical approach

The analyses described in the following sections, will be performed using the Safety analysis set, 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.

Occurrence of AEs, SAEs, and AESIs as well as ECG abnormalities, laboratory abnormalities and changes in vital signs through Day 29 will be displayed in the form of summaries and listings, where appropriate. Further details are provided below.

4.2.2.2.1. Adverse Events

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

Adverse events 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 and Non-Serious Drug-related AEs. The number and percentages of participants with the event will be summarised 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.

4.2.2.2.2. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for the purpose of analyses:

- Infusion-related reactions (IRR) including hypersensitivity reactions; reactions on same day as infusion
- Injection site reactions
- Immunogenicity related adverse drug reactions
- Adverse events potentially related to antibody-dependent enhancement of disease

All AESIs will be recorded in CRF. For reporting purposes, a comprehensive list, including the MedDRA terms which contribute to each of the AESI groups will be used. It will be based on the current MedDRA version and the safety review team (SRT) agreements in place at the time of reporting. This will be finalized prior to unblinding.

For each 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.

4.2.2.2.3. 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 for each cohort.

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 DAIDS criteria listed in Section 6.2.3. The increases on maximum grades will summarized by visit for each parameter. The shifts on maximum grade at each visit will also be summarized for each parameter in a separate table. 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. All tests that have been specified in the protocol will be included in listings, along with flags to indicate the abnormalities ("low" and "high") and toxicity grades above 0. Also, participants who had shifts from baseline in maximum grades will be listed. 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.

4.2.2.2.4. Vital Signs

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

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.

4.2.2.2.5. Electrocardiograms

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

If Respiration Rate (RR) interval (msec) is not provided directly, then RR can be derived as:

If QTcB is machine read and QTcF is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value and should not be derived.

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 by visit. In addition, the maximum QTcF values post baseline and overall worst case post-baseline relative to baseline will be summarized in a table by categories of “≤ 450 msec”, “451-480 msec”, “481-500 msec”, “≥ 501 msec”, and “missing”.

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.

4.2.2.2.6. Extent of Exposure

Exposure data including duration of administration and interrupted treatment along with reasons for interruption will be summarized in a table. Listings of data on participant exposure will also be generated for each study Part.

4.2.2.2.7. Other Safety Measures

For participants who meet liver chemistry stopping criteria, follow-up assessments after liver stopping or monitoring event are required. Liver event details should be captured in the appropriate case report forms (CRF). Physical examination, pregnancy tests, follicle-stimulating hormone (for female participants with non-childbearing potential only), serum or urine drug screen (including alcohol) and serology results will be captured in CRF. Participant listings will be provided. Scatter plots of maximum vs. baseline for ALT, and maximum total bilirubin vs. maximum ALT will also be generated.

4.3. Secondary Endpoint(s)

4.3.1. Pharmacokinetics

4.3.1.1. Definition of Endpoint(s)

Serum pharmacokinetic parameters will be calculated using the same standards listed in Section 4.2.1.1. Pharmacokinetic parameters listed below in Table 2 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.

Table 2 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
$\%AUC_{exp}$	Area under the concentration-time curve extrapolated from time t to infinity as a percentage of total AUC
λ_z	Terminal rate constant
AUC_{inf}	Area under the concentration-time curve extrapolated to infinity calculated as: $AUC_{inf} = AUC_{0-t} + C(t) / \lambda_z$ Where AUC_{0-t} is the area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_t); λ_z is the first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
AUC_{last}	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_t)
CL	Apparent total body clearance of the drug from serum
C_{max}	Maximum observed serum concentration, determined directly from the concentration-time data.

Parameter	Parameter Description
T_{max}	Time to reach $C_{max,}$ determined directly from the concentration-time data.
$T_{½}$	Apparent terminal phase half-life will be calculated as: $t_{½} = \ln 2 / \lambda_z$
T_{last}	Time to reach the last quantifiable concentration (C_t)
V_{ss}	Apparent volume of distribution at steady state
V_z	Apparent volume of distribution during terminal phase

NOTES: Additional parameters may be included as required.

4.3.1.2. Main Analytical Approach

The secondary pharmacokinetic analyses will be based on the PK analysis set, 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.

4.3.1.2.1. Drug Concentration Measures

Concentrations of sotrovimab in serum will be listed through Week 18 for all participants by actual time and summarised by ethnicity (i.e. Japanese or Caucasian) for Part 1 and Part 2 separately. Standard summary statistics will be calculated (i.e. n, geographic mean, arithmetic mean, standard deviation, median, minimum and maximum). The same outputs as specified in Section 4.2.1.2 are planned. Also, details are provided in OPS Section 2 List of Data Displays/ TFL Table of Content for details.

4.3.1.2.2. Derived Pharmacokinetic Parameters

Parameters will be summarised 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 ethnicity. Data display specifications for derived PK parameter summaries and listings are provided in OPS Section 2 List of Data Display/ TFL Table of Content.

Untransformed Data: $T_{max,}$ $T_{last,}$ $t_{½,}$ λ_z	n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum
Log_e-transformed Data: AUC_{inf}, AUC_{last}, $C_{max,}$ $V_{z,}$ $V_{ss,}$ CL,	n, geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and $\%CV_b$ (percent coefficient of variation between groups)

The following statistical analyses will also be performed for the derived PK parameters only if PK concentration levels exceed the lower level of Quantification (LLQ) for the data to be available.

Ethnicity comparisons will be performed at Week 18 for both Part 1 (IV) and Part 2 (IM). This will be done for each part separately at the planned final Week 18 SAC. Absolute bioavailability comparison will also be conducted.

1. Ethnicity Comparison
Endpoint(s)
• C_{max}, AUC_{inf}
Model Specification

• log_e-transformed values of endpoints will be statistically analyzed separately using ANCOVA with the following terms:
  ○ **Dependent variable:** C_{max}, AUC_{inf}
  ○ **Covariates:** weight, ethnicity (Japanese, Caucasian)
• Point estimates and their associated 90% confidence intervals (CI) will be constructed for the differences in PK parameter values between the Japanese and Caucasian. The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and their 90% CIs for the ratios, Japanese/Caucasian 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 ethnicity group (Japanese, Caucasian), point estimates and associated 90% confidence intervals for the ratios for each parameter will be produced in tabular format. • Plots of adjusted geometric mean ratio of test to reference ethnicity group (Japanese:Caucasian) together with 90% confidence intervals will be produced.

2. Bioavailability Assessment for Part 1 and Part 2 in final Week 18 SAC
Endpoint(s)
• AUC_{inf}

Model Specification
• log_e-transformed values of endpoints will be statistically analyzed using ANCOVA with the following terms: o **Dependent variable:** AUC_{inf} o **Covariates:** weight, ethnicity (Japanese, Caucasian), route of administration (IV, IM), Data will be analyzed for all participants in Part 1 (IV) and Part 2 (IM). • Point estimates and their associated 90% confidence intervals (CI) will be constructed for the differences in PK parameter values between the test (IM) and reference (IV) treatments. 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 administration route (IV, IM), point estimates and associated 90% confidence intervals for the ratios 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 adjusted geometric mean ratio of test to reference administration route (IM:IV) together with 90% confidence intervals will be produced.

4.3.2. Safety

4.3.2.1. Definition of Endpoint(s)

For Part 1 and Part 2, the secondary safety endpoints are:

- Occurrence of AEs through Week 18
- Occurrence of SAEs through Week 18
- Occurrence of AESIs through Week 18
- Occurrence of clinically significant abnormalities on 12-lead ECG reading through Week 18
- Occurrence of clinically significant changes in vital signs compared to baseline through Week 18

- Occurrence of clinically significant laboratory abnormalities through Week 18

4.3.2.2. Main analytical approach

The analyses will be performed using the Safety analysis set, 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.

Occurrence of AEs, SAEs, and AESIs as well as ECG abnormalities, laboratory abnormalities and changes in vital signs through Week 18 will be displayed in the form of summaries and listings, where appropriate.

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

4.4. Tertiary/Exploratory Endpoint(s)

4.4.1. Definition of Endpoint(s)

The exploratory immunogenicity endpoint is the incidence and titers (if applicable) of serum ADAs and drug-neutralizing antibodies to sotrovimab through Week 18.

Antibodies to sotrovimab will be evaluated in serum samples collected from all participants according to the Appendix 2 Schedule of Activities (SoA Section 6.3). Serum samples will be screened for antibodies binding to sotrovimab and the titer of confirmed positive samples will be reported.

4.4.2. Main analytical approach

The analyses will be performed using the Safety analysis set, 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 ADA, drug-neutralizing antibodies to sotrovimab and titres will be summarized by visit. All immunogenicity data will be listed at the planned primary Day 29 Part 1 analysis, the Day 29 Part 2 analysis (if applicable) and the final Week 18 analysis.

4.5. Other Analyses

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.

Furthermore, information of coronavirus infection diagnosis and assessment will also be collected in the eCRF. A summary of the following COVID-19 assessments will be produced: Case Diagnosis Diagnosis (i.e., confirmed, probable, suspected), COVID-19 Test performed (i.e., Yes/No), and Results of the COVID-19 test (i.e., Negative, Positive,

Indeterminate) for participants with ssuspected, probable or confirmed COVID-19 case diagnosis.

A listing of all participants with COVID-19 Assessments and Symptom Assessments will also be generated.

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

4.6. Interim Analyses

No interim analyses are planned for either Part 1 or Part 2 in the study.

4.7. Planned Analyses

Once the last participant recruited in Part 1 completes the primary assessment (Day 29) the data will be formally unblinded in the systems to allow a readout of the primary endpoints for Part 1. This will be considered as the Part 1 Day 29 SAC. If a Day 29 analysis is agreed for Part 2, the same approach will be followed for Part 2 once the last participant recruited in Part 2 completes the Day 29. This will be considered as the Part 2 Day 29 SAC.

Part 1 and Part 2 participants will continue to complete the remaining scheduled assessments up to Week 18. The final planned analyses will be performed after all participants have completed Week 18. This will be considered the final Week 18 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 CDISC reporting standards based on the final SDTM and ADAM datasets.

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 3.

Table 3 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Section 1.2 Schema and Section 9.5 Interim Analysis of the protocol (Dated: 27-MAY-2021), specify that only primary endpoints are planned to be reported for the Part 1 Day 29 SAC.	If immunogenicity data are available, the exploratory immunogenicity endpoints will also be reported in the Part 1 Day 29 SAC in addition to primary endpoints. Similarly, for the subsequent planned SAC deliverables.	Immunogenicity data (if available) is required for submission purposes.

5. SAMPLE SIZE DETERMINATION

No formal statistical techniques were used to calculate the sample size for this study.

In each Part, a maximum of 24 participants will be randomized to achieve 20 evaluable participants in Part 1 and 20 evaluable participants in Part 2. In Part 1, 8 Japanese and 8 Caucasian participants will be randomized to the IV sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm. In Part 2, 8 Japanese and 8 Caucasian participants will be randomized to the IM sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm. The number of participants randomized to each arm will provide acceptable precision for PK estimation.

Note: "Evaluable" is defined as a participant who has been randomized, has been exposed to study intervention and who has at least 1 non-missing PK assessment (including non-quantifiable samples) – i.e., PK sample collected and analyzed.

If participants permanently discontinue the study before Day 29, additional participants may be enrolled as replacements and assigned to the same cohort and treatment, at the discretion of the Sponsor or designee, in consultation with the investigator.

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 unless otherwise specified.

6.1.1. Participant Disposition

Study status for all original and replacement 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 18 visit. A separate table for study status will also be produced by relations to 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 on the Screened analysis set. Participants with screen failure and reason for screen failure will be listed.

Number of participants in each analysis set (Screened, Enrolled, Randomized, Safety, and PK) will be summarized by treatment arm in a table. This table will be based on Screened analysis set. A listing of participants excluded from any analysis set will also be provided for the Screened analysis set.

A summary table will be generated providing the count of participants in each treatment arm included for enrolled, safety and PK analysis sets respectively (see Section 3 for definition of analysis sets) and they will be displayed by ethnicity and site ID.

Listings of rescreened, discontinued, and participants for whom the treatment blind was broken will be generated respectively.

6.1.2. Demographic and Baseline Characteristics

Demographic data include year of birth, gender, race, ethnicity, height in centimetres, body weight in kilograms, and body mass index (BMI). Demographic data will be summarized and listed for the Safety analysis set. Age ranges will be summarized in a separate table. 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.

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 categorised 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 will be collected in CRF. A summary table will be generated for substance use including smoking history, current smoking status, days smoked All substance use data will also be displayed in a listing.

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-randomisation values. If either the baseline or post-randomisation 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} 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
Bicarbonate, Low (mEq/L; *mmol/L*)	> 16.0 > *16.0*	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 < *8.0*
Bilirubin ***Direct Bilirubin, High***	NA	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and

Clinical Chemistry					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
					symptoms of liver failure)
Bilirubin ***Total Bilirubin, High***	< 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
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*
Creatine Kinase, High	< 3 x ULN	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
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*
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High***	< 200 < *5.18*	200 to < 240 *5.18 to* < *6.19*	240 to < 300 *6.19 to* < *7.77*	≥ 300 ≥ *7.77*	NA
LDL, Fasting, High	< 130 < *3.37*	130 to < 160 *3.37 to* < *4.12*	160 to < 190 *4.12 to* < *4.90*	≥ 190 ≥ *4.90*	NA
Magnesium15, 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*

Clinical Chemistry					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
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*
Uric Acid, High (mg/dL; *mmol/L*)	< 7.5 < *0.45*	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 ≥ *0.89*

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*
Fibrinogen, Decreased (mg/dL; *g/L*)	≥ 200 ≥ *2.00*	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 < *0.50* OR < 0.25 x LLN OR Associated with gross bleeding
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*

Hematology					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
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
Methemoglobin (% hemoglobin)	< 5.0%	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
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
Blood, Increased Hematuria	< 6 RBCs	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Protein, Increased Proteinuria	0 or trace	1+	2+	3+ or higher	NA

Vital Sign					
Parameter	**Grade 0 Normal**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Blood Pressure ***Hypertension***	< 140 mmHg systolic OR < 90 mmHg diastolic	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated

6.2.4. Criteria for 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.

The criteria listed below will be used to determine the potential clinical importance (PCI) of lab assessments.

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

In addition, the following criteria will be used to flag potential clinical importance of ECG and VS tests:

ECG Parameter	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTc	msec		>60

Vital Sign Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	<90	>160
Diastolic Blood Pressure	mmHg	<45	>100
Pulse Rate	bpm	<40	>110

6.2.5. 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

6.2.6. 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 summary statistics will be based on the calculated 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.

6.2.7. 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.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>▪ 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:
<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>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

6.3. Appendix 2 Schedule of Activities (SoA)

				W1			W2	W3	W4	W6	W8	W12	W18
	Study Visit Day ± Visit Window	**Screening[1] (up to D -28)**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15 ± 1d**	**Day 29 ± 2d**	**Day 43 ± 3d**	**Day 57 ± 4d**	**Day 85 ± 7d**	**Day 127 ± 7d**
	Admission to unit		X										
	Discharge from unit					X							
Screening	Informed consent	X											
Screening	Demographics	X											
Screening	Medical history (incl. medication/drug/alcohol/ tobacco use, allergies, illnesses, and SARS-CoV-2 infection/therapy/vaccination)	X	X[2]										
	Randomization			X									
	Study intervention administration			X									
Assessments	Full physical examination	X[3]		X		X							
Assessments	Vital Signs (BP, PR, RR, temperature, SpO_2)[4]	X		X[4]	X	X	X	X	X	X	X	X	X
Assessments	Local injection site tolerability assessment (intramuscular injections only)			X[5]	X[5]	X[5]							
Assessments	12-lead ECG[6]	X[6]		X[6]			X	X	X		X		X
Sample collection	Lab assessments (hematology, clinical chemistry, coagulation)	X		X[7]	X		X		X	X	X	X	X
Sample collection	Urinalysis and urine albumin to creatinine ratio	X		X[8]			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 NAAT	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
Sample collection	Blood sample for immunogenicity testing (anti-drug antibody and drug-neutralizing antibody)			X[8]					X			X	X
	AE review			<========== X ==========>									
	SAE review	X[11]	X[11]	<========== X ==========>									
	AESI and concomitant medication review			<========== X ==========>									

Notes
In case of early discontinuation or withdrawal (ED or EW) all Week 18 (D127) activities should be performed.

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, 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 (IV and IM), at approximately 15 minutes after the infusion is started (IV only), and at the end of infusion (IV only) or immediately after injections (IM only). Vital signs will be monitored at approximately 30 minutes, 1 hour, and 2 hours after infusion or injection (IV and IM). 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 1 hour post-dose, those with severe ISRs on Day 1 need to be assessed in-person at Day 2 *or* 3. All ISRs need to be followed by the PI to resolution.
6. Triplicate 12-lead ECGs will be collected at Screening. All other timepoints are single 12-lead ECGs (unless an abnormality is detected post-baseline, in which case triplicate ECGs are required). On Day 1 ECGs will be performed at the following timepoints: prior to administration of study intervention (IV and IM), end of infusion (IV only), and at 1 hour and 2 hours after the end of IV infusion or first IM injection. On other days, ECGs will be performed once and time-matched to the PK sample collection.
7. Day 1 lab assessments should be collected pre-dose. Hematology assessments are performed only on Day 1.
8. On Day 1, sample collection will occur pre-dose.
9. Urine or serum pregnancy test, as per local guidelines. See Section 8.3.6.
10. Day 1 sample collection will occur pre-dose (IV and IM) and at end of infusion (IV infusion only). On Day 1, samples will also be collected at 1, 2, 6, and 8 hours after the end of infusion or first IM injection. On other days, samples will be collected once at any time of the day.
11. At screening and on Day -1, only SAEs related to study participation or a GlaxoSmithKline (GSK) product will be reported.

Abbreviations: BP = blood pressure; GSK = GlaxoSmithKline; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EW = early withdrawal; IgG = immunoglobulin G; IgM = immunoglobulin M; IM = intramuscular; ISRs = injection site reactions; IV = intravenous; NAAT =nucleic acid amplification test; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-1; PR = pulse rate; RR = respiratory rate

- 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 serum 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.

6.4. Appendix 3 Clinical Laboratory Tests

The tests detailed in Table 4 will be performed by the 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 4 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Hemoglobin			
Coagulation	International Normalized Ratio (INR)	Prothrombin Time (PT)	Activated Partial Thromboplastin Time (PTT)	
Clinical Chemistry[1]	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	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, or leukocyte esterase is abnormal) • Urine creatinine and urine albumin			

Laboratory Assessments	Parameters
Pregnancy testing	• Highly sensitive serum/plasma or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of non-childbearing potential 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 Section 7.1 and Protocol 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
ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUC_{D1-29}	AUC from Day 1 predose to Day 29
AUC_{inf}	AUC extrapolated to infinity
BLOQ	Below the Limit of Quantification
BMI	body mass index
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
CV_b	Coefficient of Variation (Between)
C_{D29}	Serum concentration on Day 29
C_{max}	Maximum observed concentration
CRF	Case Record Form
DAIDS	Division of Acquired Immune-deficiency Syndrome
ECG	Electrocardiogram
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IEC	Independent Ethics Committees
INR	International Normalized Ratio
IRB	Institutional review board
IWRS	Interactive Web Response System
MCH	Mean Corpuscular Hemoglobin
MCV	Mean corpuscular volume
OPS	Output and Programming Specification
PK	Pharmacokinetic
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RBC	Red blood cells
SAC	Statistical Analysis Complete
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model

Abbreviation	Description
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of Activities
SOC	System order class
SpO_2	Oxygen saturation
PT	Preferred term
PTT	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
Vir	Vir Biotechnology, Inc.
WBC	White blood cells
λ_z	Terminal phase rate constant

Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin

7. REFERENCES

GlaxoSmithKline Document Number TMF-13788149: A Phase I, single-blind, randomized, single-dose clinical pharmacology study to investigate the pharmacokinetics, safety, and tolerability of sotrovimab vs placebo by intravenous or intramuscular administration in healthy Japanese and Caucasian participants, 27MAY2021