Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Phase 3 randomized, multi-center, open label study to assess the efficacy, safety, and tolerability of monoclonal antibody VIR-7831 (sotrovimab) given intramuscularly versus intravenously for the treatment of mild/moderate coronavirus disease 2019 (COVID-19) in high-risk non-hospitalized patients

Study Number: VIR-7831-5008 (GSK Study 217114)

Compound Number: VIR-7831 (sotrovimab; GSK4182136)

Abbreviated Title: Intramuscular VIR-7831 for mild/moderate COVID-19

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

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Version history

SAP Version (Approval Date)	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0 (08-Jun-2021)	Amendment 1 (05-May-2021)	Not Applicable	Original version
2.0 (25-Oct-2021)	Amendment 3 (04-Oct-2021)	• Definition of ITT analysis set changed to match that in the protocol • Update to hypothetical estimand to detail key inclusion/exclusion criteria that lead to exclusion from population • Details of planned and ad hoc interim analyses added • Removal of 250mg IM dose from analyses and testing hierarchy • Region and vaccination status removed as covariates from analysis models, and the 12-17 years and 18-64 years age groupings combined in the age group covariate. • Methods for imputing COVID-19 progression status and viral load data corrected and clarified • Details added for cut-point used to define persistently high viral load • Inclusion of long COVID exploratory endpoint • Amend Week 24 timepoint to Week 36 due to increased length of follow-up in the study	Clarifications made to language in SAP to better align to language used in protocol amendments. 250mg IM arm removed from analyses and testing hierarchy due to being permanently discontinued from study at ad hoc interim analysis. Model covariates amended due to small numbers of patients in non-US regions, small proportion of fully/partially vaccinated participants, and small number of participants <18 years.

SAP Version (Approval Date)	Protocol Version (Date) on which SAP is Based	Change	Rationale
		• Addition of Kaplan-Meier plot summarizing time to undetectable viral load • Addition of new subgroup and PK-PD analyses.	

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study VIR-7831-5008. Details of the final Day 29 efficacy and safety analyses and 36-Week Safety Follow-Up analyses are provided.

Additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the efficacy of two dose levels of intramuscular sotrovimab versus intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Hospitalization > 24 hours for acute management of illness due to any cause OR • Death
Secondary	
Safety • Describe the safety and tolerability of intramuscular and intravenous sotrovimab	• Occurrence of adverse events (AEs) • Occurrence of serious adverse events (SAEs) • Occurrence of adverse events of special interest (AESI) • Occurrence of disease-related events
• Assess the immunogenicity of sotrovimab	• Incidence and titers (if applicable) of serum anti-drug antibody (ADA) to sotrovimab
Efficacy • Evaluate the efficacy of two dose levels of intramuscular versus intravenous sotrovimab on the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR • Hospitalization for acute management of illness for any duration and for any cause OR • Death

Objectives	Endpoints
• Evaluate the efficacy of two dose levels of intramuscular versus intravenous sotrovimab in preventing COVID-19 respiratory disease progression	• Development of severe and/or critical respiratory COVID-19 as manifested by requirement for respiratory support (including oxygen) at Day 8, Day 15, Day 22, and Day 29
• Compare the virologic activity of sotrovimab given IM (two dose levels) or IV in reducing SARS-CoV-2 viral load	• Mean area under the curve of SARS-CoV-2 viral load in nasal secretions as measured by qRT-PCR from Day 1 to Day 8 (AUC_{D1-8}) • Change from baseline in viral load by qRT-PCR at Day 8 • Proportion of participants with a persistently high SARS-CoV-2 viral load at Day 8 by qRT-PCR
Pharmacokinetics • Assess the pharmacokinetics (PK) of sotrovimab in serum following IV and IM (two dose levels) administration	• IV and IM sotrovimab pharmacokinetics (PK) in serum
Exploratory	
• Describe the effect of two doses levels of intramuscular versus intravenous sotrovimab on incidence and duration of time on total hospital length of stay (LOS), incidence and duration of time on a ventilator, and ICU length of stay	• Incidence of hospitalization through Day 29 • Total hospital LOS • Proportion of participants requiring ICU stay or mechanical ventilation through Day 29 • Total ICU LOS
• Monitor SARS-CoV-2 resistant mutants against sotrovimab	• SARS-CoV-2 resistance mutants to sotrovimab at baseline • Emergence of viral resistance mutants to mAb by SARS-CoV-2
• Compare the virologic activity of sotrovimab given IM (two dose levels) or IV in reducing SARS-CoV-2 viral load	• Change from baseline in viral load in nasal secretions by qRT-PCR during follow-up period at Day 5, Day 11, Day 15, Day 22 and Day 29

Objectives	Endpoints
	• Undetectable SARS-CoV-2 in nasal secretions by qRT-PCR at Day 3, Day 5, Day 8, Day 11, Day 15, Day 22 and Day 29 • Mean area under the curve of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 5 (AUC_{D1-5}) and Day 1 to 11 (AUC_{D1-11})
• Compare the effect of different sample collection methods in SARS-CoV-2 viral load (e.g. nasopharyngeal swab, saliva)	• SARS-CoV-2 viral load measured by qRT-PCR
• Evaluate the effect of sotrovimab on the development of SARS-CoV-2 antibodies	• SARS-CoV-2 anti-N antibody at Day 1 and Day 29
• Describe the effect of sotrovimab on Long COVID symptoms	• Incidence and severity of Long COVID symptoms at Week 12, Week 24 and Week 36

Primary estimand

The primary efficacy endpoint will primarily be assessed using an estimand that uses a hypothetical strategy to deal with the main intercurrent events. The estimand is described by the following attributes:

- Population: All participants in the Intent-to-Treat (ITT) analysis set excluding participants who did not meet key inclusion/exclusion criteria (see section 4.2.2.1).
- Endpoint: Progression of COVID-19 through Day 29 as defined by hospitalization > 24 hours for acute management of illness due to any cause or death
- Summary measure: Absolute difference in the proportion of participants meeting the primary endpoint
- The anticipated intercurrent events are:
  - Not receiving randomized treatment or an alternative study treatment (i.e. treatment misallocation)
  - Discontinuation of study intervention as described in Protocol Section 7.1.
  - Use of medication not permitted during the study as listed in Protocol Section 6.8.1 up to Day 29

All intercurrent events will be handled using a hypothetical strategy where data collected after the occurrence of an intercurrent event will be excluded from the analysis, i.e. assuming the intercurrent event had not occurred.

Rationale for estimand: A hypothetical estimand is used as this is considered more conservative than treatment policy and therefore more appropriate for a non-inferiority comparison.

Supplementary Estimand for the Primary Endpoint

A supplementary estimand will be conducted based on all participants in the ITT analysis set by handling all intercurrent events with a treatment policy strategy (i.e. regardless of the intercurrent events occurring), with all the other attributes being the same as in the primary estimand. To estimate this estimand, all data collected in the ITT analysis set up to Day 29 will be included in the analysis.

Estimands for Key Secondary Endpoints

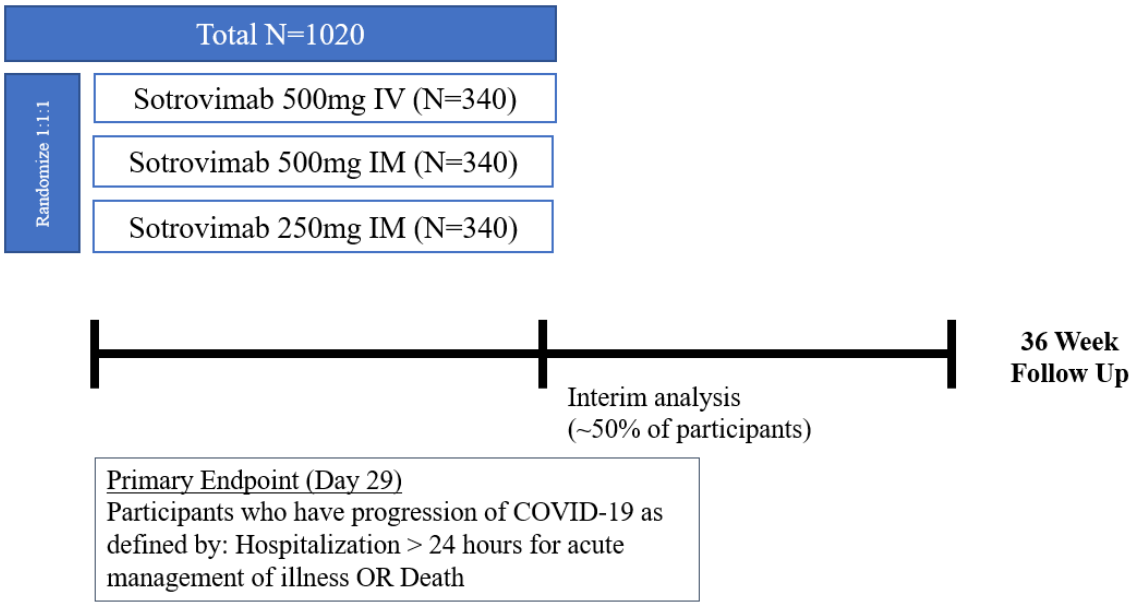
The estimand for the secondary endpoint 'Mean area under the curve of SARS-CoV-2 viral load in nasal secretions as measured by qRT-PCR from Day 1 to Day 8 (AUC_{D1-8})' is described by the following attributes:

- Population: All participants in the Virology analysis set, as defined in Section 3
- Summary measure: Treatment ratio (IM/IV) of mean $\log_{10}$ AUC_{D1-8}
- Intercurrent events: Death and use of medication not permitted during the study as listed in Protocol Section 6.8.1 up to day 8
    - Strategy for Death: Composite strategy, where for participants who die prior to Day 8, the AUC_{D1-8} viral load value will be imputed using the worst AUC_{D1-8} viral load value from other participants in the same treatment arm.
    - The strategy for all the other intercurrent events (as applicable for this endpoint) will be treatment policy where data will be reported as captured.

The secondary endpoint 'Progression of COVID-19 through Day 29 as defined by visit to a hospital emergency room for management of illness OR Hospitalization for acute management of illness for any duration and for any cause OR Death' will be assessed using a hypothetical estimand as described for the primary endpoint. A supplementary treatment policy estimand will also be assessed using the same approach as the treatment policy estimand for the primary endpoint.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• This study is a Phase 3 randomized, multi-center, open label, non-inferiority study of intramuscular (IM) versus intravenous (IV) administration of sotrovimab, a monoclonal antibody (mAb) against SARS-CoV-2 for the treatment of mild/moderate COVID-19 in participants aged 12 years and older at high risk of disease progression. • Approximately 1020 participants will be enrolled and randomized 1:1:1 to receive a single 500 mg IV infusion of sotrovimab, a single 500 mg IM injection of sotrovimab, or a single 250 mg IM injection of sotrovimab. • Participants with early, mild/moderate COVID-19 who are not on supplementary oxygen and are at risk for disease progression will receive an IV infusion or IM injection of sotrovimab. The intravenous sotrovimab dose will be 500 mg and will be infused over 15 minutes. The intramuscular sotrovimab dose will be either 250 mg or 500 mg given at a single timepoint. The 250 mg IM dose will be given either as a single 250 mg (4ml) injection in the dorsogluteal muscle or as two 2ml injections in each deltoid muscle. The 500 mg IM dose will be administered as two 4ml injections in each dorsogluteal muscle. • After IV infusion or IM injection, participants will be monitored for 30 minutes with vital signs assessments performed every 15 minutes. Injection site reaction assessments, for IM arms only, will be performed at 15 and 30 minutes after injection.

Overview of Study Design and Key Features	
	• All participants will be actively monitored on an outpatient basis with frequent collection of nasopharyngeal swabs for virology and blood draws for PK sampling and safety labs, as well as in-clinic evaluations at Weeks 1, 2, 3, 4, 12, 20 and 24 as detailed in the Schedule of Activities. • Starting at Week 8, participants will be monitored monthly via phone call or in-clinic evaluation to assess for the incidence and severity of subsequent COVID-19 illness, if any, for a total of 36 weeks from dosing.
Study intervention	• VIR-7831 500mg IV or VIR-7831 500mg IM or VIR-7831 250mg IM • All participants will receive SoC as per institutional protocols, in addition to the study intervention.
Study intervention Assignment	• Participants with early, mild/moderate COVID-19 who are not on supplementary oxygen and at risk for disease progression will be randomised 1:1:1 to receive a single dose of VIR-7831 500mg IV, VIR-7831 500mg IM or VIR-7831 250mg IM. Participants will be stratified based on: 1. Age: 12-17 years old, 18-64 years old, and ≥65 years old 2. COVID-19 Vaccination History: receipt of any COVID-19 vaccine (yes, no) 3. Region of the world (North America, South America, Europe, South Asia, Rest of Asia, Rest of the World). • All participants will be centrally randomized using an Interactive Web Response System (IWRS). • Participants will receive sotrovimab either by IM or IV directly from the investigator or designee, under medical supervision. The date and start and stop times of the dose administered will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
Interim Analysis	• The Joint Safety Review Team (JSRT) comprising individuals from Vir and GSK will review safety data at regular intervals throughout the conduct of the study. Details of the JSRT process is recorded in relevant SRT documents. • If, during its regular scheduled review of study data, the JSRT identifies a potential safety signal, Vir may request an ad hoc meeting of the IDMC to review data for further evaluation. • An interim analysis was planned (see Protocol Amendment Version 2) once 50% of the planned number of participants had completed the Day 29 assessment. However, prior to the time of the planned analysis, the JSRT noted a discrepancy in the rate of progression to hospitalization occurring in

Overview of Study Design and Key Features	
	the 250mg IM arm compared with the 500mg IM and IV arms. Upon review of the cumulative data, the JSRT made the decision to pause enrollment into the 250mg IM arm on 04-August-2021 and escalated the issue to the IDMC. • An ad hoc meeting of the IDMC was called on 11-August-2021 and based upon their review of the data, the IDMC concurred that enrollment in the 250mg IM arm should be discontinued. As this ad hoc IDMC meeting occurred prior to the timepoint when the formal interim analysis would have occurred and concluded with discontinuing one arm of the study combined with an unexpected rapid increase in the rate of enrollment, it was not feasible to conduct the formal interim analysis. • Therefore, data for the 250mg IM arm will be summarised only and not used for any statistical hypotheses tests or analyses.

2. STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate the efficacy of IM sotrovimab versus IV sotrovimab in preventing the progression of mild/moderate COVID-19 in a non-inferiority comparison.

The primary endpoint is progression of COVID-19 through Day 29 as defined by hospitalization > 24 hours for acute management of illness OR death.

Denoting the proportions of participants with progression of COVID-19 by Day 29 in the sotrovimab 500 mg IM arm, sotrovimab 250 mg IM arm and sotrovimab 500 mg IV arm as P_{IM500}, P_{IM250} and P_{IV500}, respectively, then the null (H_0) and alternative (H_A) hypotheses are as follows using a non-inferiority margin of 3.5% (per feedback from the FDA, as mentioned in protocol section 4.2) on the risk difference scale:

(1) Sotrovimab 500 mg IM vs sotrovimab 500 mg IV:

- H_0: $P_{IM500} - P_{IV500} \geq 3.5\%$. H_A: $P_{IM500} - P_{IV500} < 3.5\%$

(2) Sotrovimab 250 mg IM vs sotrovimab 500 mg IV:

- H_0: $P_{IM250} - P_{IV500} \geq 3.5\%$. H_A: $P_{IM250} - P_{IV500} < 3.5\%$

2.1. Multiplicity Adjustment

Hypotheses (1) and (2) above will be tested using the primary estimand according to the hierarchical testing principal as follows:

- If the null hypothesis for (1) is rejected, i.e., the upper bound of the two-sided 95% confidence interval for the risk difference between sotrovimab 500 mg IM and

sotrovimab 500 mg IV is less than the pre-specified 3.5% non-inferiority margin, then hypothesis for (2) will be tested.
- If the null hypothesis for (1) is not rejected, then hypothesis for (2) will not be tested.

Below is a summary of possible outcomes of the hierarchical testing procedure:

Which Null Hypothesis is Rejected	Non-inferiority Declared For
Hypotheses (1) and (2)	Both sotrovimab 500 mg IM and sotrovimab 250 mg IM (vs. sotrovimab 500 mg IV)
Hypothesis (1) but Not (2)	Only sotrovimab 500 mg IM vs. sotrovimab 500 mg IV
Hypothesis (1) is NOT rejected (Null hypothesis for (2) won't be tested in this case)	Neither sotrovimab 500mg IM nor sotrovimab 250mg IM (vs sotrovimab 500mg IV)

Two secondary endpoints will be formally analysed:

1) Mean area under the curve of SARS-CoV-2 viral load in nasal secretions as measured by qRT-PCR from Day 1 to Day 8 ($AUC_{D1\text{-}8}$). Each IM dose will be assessed for equivalence to IV based on the two-sided 90% confidence interval for the treatment ratio falling within equivalence bounds of 0.5 to 2.0.
2) Progression of COVID-19 through Day 29 as defined by visit to a hospital emergency room for management of illness OR Hospitalization for acute management of illness for any duration and for any cause OR Death. Each IM dose will be assessed for non-inferiority vs IV using a non-inferiority margin of 3.5% on the risk difference scale.

The testing of the two secondary endpoints above is adjusted for multiplicity by using the following hierarchy:

- Secondary endpoint (1) will only be tested if non-inferiority is achieved for sotrovimab 500 mg IM vs. sotrovimab 500 mg IV and sotrovimab 250 mg IM vs. sotrovimab 500 mg IV comparisons for the primary endpoint.
- Secondary endpoint (1) will be tested in the same sequential way as the primary endpoint i.e If the null hypothesis for sotrovimab 500 mg IM vs. sotrovimab 500 mg IV is rejected, then the null hypothesis for sotrovimab 250 mg IM vs. sotrovimab 500 mg IV will be tested. If the null hypothesis for sotrovimab 250 mg IM vs sotrovimab 500mg IV for secondary endpoint (1) is rejected, then secondary endpoint (2) will be tested in the same sequential manner as secondary endpoint (1).

Given that recruitment to the sotrovimab 250 mg IM arm was permanently discontinued following the *ad hoc* interim analysis on 11-Aug-2021, the sotrovimab 250 mg IM arm will not

be formally compared to the sotrovimab 500 mg IV arm. Therefore only hypotheses for primary and secondary endpoints related to the 500 mg IM arm will be formally tested in the above framework and hypotheses related to the 250 mg IM arm are removed from the testing hierarchy.

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
Randomized	All participants who were randomized. Participants will be analyzed according to the route of administration and dose level they were randomized to: sotrovimab IM (500 mg), sotrovimab IM (250 mg) or sotrovimab IV (500 mg).	Study Population
Intent-to-Treat (ITT)	All participants who were randomized. Participants who were randomized under Protocol Amendment Version 1 and were immunocompetent and fully vaccinated at randomisation will be excluded. Participants will be analyzed according to the route of administration and dose level they were randomized to: sotrovimab IM (500 mg), sotrovimab IM (250 mg) or sotrovimab IV (500 mg).	Study Population Efficacy
Safety	All randomized participants who are exposed to study intervention. Participants will be analyzed according to the route of administration and dose level they actually received: sotrovimab IM (500 mg), sotrovimab IM (250 mg) or sotrovimab IV (500 mg).	Study Population Safety
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analyzed according to the route of administration and dose level they actually received.	PK

Analysis Set	Definition / Criteria	Analyses Evaluated
Virology	All participants in the ITT analysis set with a lab confirmed quantifiable baseline nasopharyngeal swab at Day 1. Participants will be analyzed according to the route of administration and dose level they were randomized to: sotrovimab IM (500 mg), sotrovimab IM (250 mg) or sotrovimab IV (500 mg). This will be the primary analysis set for virology.	Efficacy (Virology)

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The ITT Analysis Set will be used for all Study Population analyses and Efficacy analyses, unless otherwise specified A subset of the ITT analysis set will be used for the primary estimand, excluding participants who did not meet key inclusion/exclusion criteria (see 4.2.2). The Safety Analysis Set will be used for selected Study Population summaries and all safety analyses. The PK analysis Set will be used for all PK analyses. Virology analysis set will be used for all Virology analyses.

In the case of a difference between the stratification assigned at the time of randomization and the data collected in the eCRF, the analyses will be performed based on the data collected in the eCRF, not the assigned stratum at randomization. All analyses will be adjusted for treatment group (sotrovimab 500mg IV, sotrovimab 500mg IM), derived age group (<65 years old, ≥65 years old, see Section 6.2.7), and gender (female, male). Stratification factors of region and vaccination status are not included as covariates due to the small number of non-US and partially/fully vaccinated participants in the ITT analysis set. In addition the 12-17 years old and 18-64 years old categories are combined due to the small number of participants in the 12-17 years old category.

In the case of model convergence issues, if one category dominates within a particular covariate then that covariate may be considered for removal from the model.

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

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. For log-transformed data (e.g. AUC) descriptive statistics will present the geometric mean, standard deviation (SD of log-transformed data) and coefficient of variation. Categorical data will be summarized as the number and percentage of participants in each category.

Efficacy data will be reported according to nominal time of clinical visits unless otherwise stated. Hospitalization status, oxygen supplementation and healthcare resource utilization use will be slotted against the clinical visit date for summaries and analyses by visit.

All data will be reported according to the nominal time of clinic visits and assessments as specified in the protocol unless stated otherwise:

- Day 8, Day 11, Day 15, Day 22, where data within ±1 days of the target day may be used if data is not recorded on the actual day
- Day 29, where data within ±2 days of the target day may be used if data is not recorded on the actual day
- Day 57, where data within ±4 days of the target day may be used if data is not recorded on the actual day
- Day 85, Day 113, Day 141, Day 169, Day 197, Day 224, Day 252 where data within ±7 days of the target day may be used if data is not recorded on the actual day

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits and the screening visit. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For endpoints assessed using an analysis set other than the Safety analysis set, the baseline value for subjects who are randomised and not dosed will be the latest assessment with nominal visit on or prior to Day 1.

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

4.1.3. Missing Data Handling Rules

- Missing data can occur due to study withdrawal or participants lost to follow-up before the completion of the study or due to intermittent missing values (i.e. data between two non-missing assessments).
- In addition, for the hypothetical estimands of the primary and secondary COVID-19 progression endpoints, data collected after the occurrence of an intercurrent event will be excluded from the analysis and will therefore be set to missing.
- For the primary and secondary COVID-19 progression endpoints, missing data will be imputed under a missing at random (MAR) assumption using a multiple imputation (MI) model. More details are provided in Section 6.2.8.

- For all other endpoints, a treatment policy strategy will be used for all intercurrent events where all data captured will be included in the summary and analysis, unless otherwise stated.

The following rules will be applied to viral load endpoints:

- The imputation logic when a sample is reported as 'NEG' (below lower-limit of detection) or '<2.08' (below lower-limit of quantification) is to impute as 0.5 x 120 copies/ml = 60 copies/ml = 1.78 $\log_{10}$ copies/ml
- Subjects who die prior to Day 8 (or Day 5 or Day 11), their AUC viral load value will be imputed using the worst AUC viral load value from other subjects in the same treatment arm who have completed Day 8 (5/11) and have a valid AUC(D1-8)/(D1-5)/(D1-11).
- If Day 8 assessment alone is missing but Day 5 and Day 11 assessments are available, the Day 8 will be imputed using linear interpolation between Day 5 and Day 11. AUC will be calculated then.
- If more than 2 consecutive assessments are missing prior to and including Day X, then the AUC(D1-X) will not be calculated.
- If a subject is lost to follow-up prior to Day X, then AUC(D1-X) will be set to missing.

4.2. Primary Endpoint Analyses

4.2.1. Definition of Primary Endpoint

The primary endpoint is the progression of COVID-19 through Day 29 as defined by hospitalization > 24 hours for acute management of illness due to any cause OR death.

The primary efficacy endpoint will primarily be assessed using an estimand that uses a hypothetical strategy to deal with the main intercurrent events as detailed in section 1.1.

4.2.2. Main analytical approach

The primary analysis will be conducted on the ITT analysis set, excluding participants who did not meet key inclusion/exclusion criteria (see section 4.2.2.1). All intercurrent events (see below) will be handled using a hypothetical strategy for the primary estimand, i.e. assuming the intercurrent event had not occurred.

The primary endpoint will be summarized using counts and percentages of the number of participants who have progression of COVID-19. The proportion of participants meeting the primary endpoint will be compared for sotrovimab 500 mg IM vs sotrovimab 500 mg IV using a 3.5% non-inferiority margin on the risk difference scale as per section 2.

The proportion of participants meeting the primary endpoint will be compared between treatments using a generalized linear model (GLM) from the binomial family with identity link, adjusted for treatment group (sotrovimab 500mg IV, sotrovimab 500mg IM), derived age group (<65 years old, ≥65 years old, see Section 6.2.7), and gender (female, male).

The absolute risk difference and associated 95% CI will be computed to test for non-inferiority in hypothesis (1).

Covariates may be removed from the model if it fails to converge as described in section 4.1.1. If the model still does not converge a GLM assuming a normal distribution for the endpoint and with identity link will be used, adjusted for the covariates above. If no events are observed on either treatment arm, the Farrington-Manning test will be used to compare arms.

The anticipated intercurrent events are:

- Not receiving randomized treatment or an alternative study treatment (i.e. treatment misallocation)
- Discontinuation of study intervention as described in Protocol Section 7.1.
- Use of medication not permitted during the study as listed in Protocol Section 6.8.1 up to day 29

Events are only deemed to be intercurrent events if they occur before occurrence of the primary endpoint. Data observed in the period following an intercurrent event (i.e. from the study day following the intercurrent event) will be excluded from the analysis. Data from this period will be assumed "missing at random" (MAR).

For participants that withdraw from the study and do not meet the primary endpoint at the time of withdrawal, data in the post-withdrawal period will also be assumed MAR.

Details of the method for multiple imputation is described in section 6.2.8.

4.2.2.1. Key Inclusion/Exclusion Criteria

Type	Category	Criteria
Inclusion	5.1.2. Type of Participant and Disease Characteristics	1. Participants who have a positive SARS-CoV-2 test result within 7 days of randomization (by any validated diagnostic test e.g. RT-PCR, antigen based testing on any specimen type)
		4. Participant to be dosed less than or equal to 7 days from onset of symptoms to dosing day (D1) Note: Participants will only be excluded if ≥9 days since dosing.
Exclusion	5.2.1. Medical Conditions	1. Currently hospitalized or judged by the investigator as likely to require hospitalization in the next 24 hours Note: Participants will only be excluded if hospitalized at baseline per eCRF form.
	5.2.2. Prior/Concurrent Clinical Study Experience	5. Enrollment in any investigational vaccine study within the last 180 days or any other investigational drug study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer

		6. Enrollment in any trial of an investigational drug, vaccine or device study for SARS-CoV-2/COVID-19 within 90 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer
	5.2.3. Other Exclusions	7. Immunocompetent individuals who are fully vaccinated against SARS-CoV-2. A person is considered fully vaccinated if at least 14 days have passed since receiving the final dose in a COVID-19 vaccine series.
		8. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.

4.2.3. Additional estimands

A supplementary estimand will be conducted in the ITT analysis set by handling all intercurrent events with a treatment policy strategy (i.e. regardless of the intercurrent events occurring), with all the other attributes being the same as in the primary estimand. To estimate this estimand, all data collected in the population of interest up to Day 29 will be included in the analysis. Missing data due to participant withdrawal from study will be handled in the same manner as the primary estimand.

4.2.4. Sensitivity analyses

To assess the sensitivity of the results to the missing data, a tipping point analyses will be performed for the hypothetical and treatment policy estimands. The underlying response rate among those subjects with missing response status in each arm will be varied ranging between 0 and 1. This analysis will be two-dimensional, i.e. it will allow for assumptions about the assumed response rate (and thus missing outcomes) in the two treatment arms to vary independently. For combinations of the assumed response rates in the arms, the number of additional responders among subjects with missing response will be imputed multiple times by drawing from a binomial distribution. The absolute difference and associated standard error for each imputed dataset will be calculated using the primary analysis model and results combined using Rubin's rules to calculate the risk difference and the 95% CI for the treatment comparison. Results will be presented via a heatmap.

In addition, a summary of the number of COVID-19 progressions through Day 29 (as defined in section 4.2.1) for the hypothetical estimand will be provided for the split by those progressions that occur <3 days and ≥3 days post-dose.

4.3. Secondary Endpoints Analyses

The secondary endpoints will be based on the ITT Analysis Set, unless otherwise specified.

4.3.1. Definition of Secondary Endpoints

4.3.1.1. Safety and tolerability

Adverse events analyses including the analysis of adverse events (AEs), serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs, including counts and percentages of participants with

- any AE
- any SAE
- any AESI

will be provided as outlined in Section 4.5.2. The Safety analysis set will be used.

Since it will not be possible to delineate in a single participant whether the hospitalization is directly related to COVID-19 complications or could be related to VIR-7831 causing more severe disease due to ADE, all hospitalizations regardless of cause will be included in the primary endpoint. However, if a hospitalization or adverse event is related to expected progression, signs, or symptoms of COVID-19 (as detailed in Section 8.4.8 of the Protocol) or if hospitalization is due to elective treatment of a pre-existing condition that did not worsen from baseline as noted in Section 10.3 of the Protocol it will not be considered as an SAE. These events will be collected and reported as SAEs only if the event is more severe than expected for the participant's current clinical status and medical history or if the investigator feels that it is related to study drug.

In addition, a summary of the number and percentage of participants with disease-related events, that is, events related to expected progression, signs, or symptoms of COVID-19, unless more severe than expected for the participant's current clinical status and medical history will be provided. These events will be captured on the disease related event CRF. This data will also be listed.

The following are examples of events NOT meeting the AE definition but will be classed and captured separately as disease progression events in the CRF:

- hypoxemia due to COVID-19 requiring supplemental oxygen
- hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices
- respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO

4.3.1.2. Immunogenicity of VIR-7831

The incidence and titers (if applicable) of serum ADA to VIR-7831 will be listed and summarized for the Week 36 safety summary in the Safety analysis set.

Additional immunologic analyses may be conducted and will be documented in a separate technical document.

4.3.1.3. Progression of COVID-19 by Day 29 (emergency room, hospitalisation for any duration or cause, death)

Progression of COVID-19 through Day 29 as defined by:

1. Visit to a hospital emergency room for management of illness

OR

2. Hospitalization for acute management of illness for any duration and for any cause

OR

3. Death

4.3.1.4. Proportion of Participants Who Progress to Develop Severe or Critical Respiratory COVID-19 at Day 8, 15, 22 and 29

Participants are defined as progressing to develop severe respiratory COVID-19 if they require supplemental oxygen either by nasal cannula, face mask, high-flow oxygen devices, or non-invasive ventilation.

Participants are defined as progression to critical respiratory COVID-19 if they require invasive mechanical ventilation or ECMO.

Participants who die prior to the timepoint of interest without first having received supplemental oxygen will be considered to have met the endpoint (composite estimand strategy).

Further detail on the severity of respiratory COVID-19 based on the proportion of participants meeting each tier of the Vir modified version of the NIAID Ordinal Scale for Clinical Improvement (Table 1) will be summarized.

Table 1 Ordinal Scale for Clinical Improvement

Ordinal Scale (Vir modified version, adapted from the Adaptive COVID-19 Treatment Trial [ACTT], 2020; referred to as National Institute of Allergy and Infectious Disease (NIAID) scale hereafter)
1) Not hospitalized, no limitations of activities
2) Not hospitalized, limitation of activities and/or requiring home oxygen [1]
3) Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)
4) Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions)
5) Hospitalized, requiring any supplemental oxygen
6) Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices
7) Hospitalized, receiving invasive mechanical ventilation or ECMO [2]
8) Death

[1] report as category 5 if using oxygen at home (unless were receiving home oxygen pre-morbidly), [2] Participant in receipt of extracorporeal membrane oxygenation (ECMO) at the time of dosing on Day 1 are excluded from the study (participants who subsequently require ECMO may continue in the study).

4.3.1.5. Reduction in SARS-CoV-2 Viral Load

Viral load will be log10-transformed prior to summary and analysis. The Virology analysis set will be used for all analyses.

Reduction of SARS-CoV-2 viral shedding will be determined by the change from baseline of SARS-CoV-2 nasal viral load at Day 8.

In addition, the SARS-CoV-2 viral load will also be assessed from the area under the curve (AUC as determined by the trapezoidal rule) of $\log_{10}$-transformed SARs-CoV-2 viral load through Days 1 to 8. AUC will be log-transformed prior to analysis.

The proportion of participants with a persistently high SARS-CoV-2 viral load (PHVL) assessed by qRT-PCR at Day 8 will also be assessed. PHVL is defined as a viral load value >4.1 $\log_{10}$ copies/ml at Day 8.

4.3.1.6. Pharmacokinetics of VIR-7831

Serum pharmacokinetic concentrations will be listed and summarized by treatment and visit in the PK analysis set. Any concentration not included in summaries should be flagged in the individual listings with an explanation for the exclusion.

Additional PK analyses, including additional exposure-response analyses, will be summarized in a separate PopPK analysis plan.

4.3.2. Main Analytical Approach

4.3.2.1. Binary Endpoints

The following secondary endpoints will be summarised/analysed as binary endpoints:

- Participants who have progression of COVID-19 (emergency room, hospitalisation for any duration or cause, death) through Day 29
- Proportion of Participants Who Progress to Develop Severe or Critical Respiratory COVID-19 at Day 8, 15, 22 and 29
- Proportion of participants with a persistently high SARS-CoV-2 viral load at Day 8 by qRT-PCR

The secondary binary endpoints will be summarized using counts and percentages.

Participants who have progression of COVID-19 (emergency room, hospitalisation for any duration or cause, death) through Day 29 will be analysed as per the primary endpoint (hypothetical and treatment policy estimands).

4.3.2.2. Continuous Endpoints

The following secondary endpoints will be summarised/analysed as continuous endpoints:

- Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8
- Area under the curve (AUC) of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 8 (AUC_{D1-8})
- Serum pharmacokinetic concentrations

Change from baseline in viral load at all visits including Day 8 will be summarised on the log10 scale. The Virology analysis set will be used.

AUC_{D1-8} for log10-transformed SARS-CoV-2 viral load will be analyzed using analysis of covariance adjusted for treatment group (sotrovimab 500mg IV, sotrovimab 500mg IM), baseline viral load, derived age group (<65 years old, ≥65 years old, see Section 6.2.7), and gender (female, male). AUC will be log-transformed prior to analysis. The treatment ratio and two-sided 90% CI for the comparison of sotrovimab 500mg IM vs sotrovimab 500mg IV will be calculated by back-transforming the corresponding estimates on the log-scale.

In addition, the following will be produced:

- Box plot of serum pharmacokinetic concentrations at Day 8, 15 and 29 vs COVID-19 progression status through Day 29 (as defined in section 4.2.1) for the hypothetical estimand, overall and by treatment group

- Summary table of Day 8 serum pharmacokinetic concentrations (n, mean, SD, median, min, max) by COVID-19 progression status through Day 29 (as defined in section 4.2.1) for the hypothetical estimand, total and by treatment group.

4.4. Exploratory Endpoints Analyses

The exploratory analyses will be based on the ITT Analysis Set, unless otherwise specified.

4.4.1. Definition of Exploratory Endpoints

4.4.1.1. Incidence of Hospitalisation through Day 29

A participant is defined as requiring hospital stay if they received any in-patient healthcare (A&E, general ward or ICU) encounter of any duration.

Data will be summarised as collected (while-alive estimand strategy) in addition to assuming participants who die prior to Day 29 to have met the endpoint (composite estimand strategy).

4.4.1.2. Total Hospital Length of Stay

A participant is defined as requiring hospital stay if they received any in-patient healthcare (A&E, general ward or ICU) encounter of any duration. A participant may have more than one period of hospital stay included in the total hospital length of stay.

Data will be summarised as collected (while-alive estimand strategy) in addition to assuming participants who die prior to Day 29 to have been in hospital from the date of death to Day 29 (composite estimand strategy).

4.4.1.3. Proportion of subjects requiring ICU stay or mechanical ventilation through Day 29

A participant is defined as being on a ventilator if they received invasive mechanical ventilation or ECMO as a form of oxygen therapy. A participant is defined as requiring intensive care if they received an intensive care unit in-patient healthcare encounter of any duration.

Data will be summarised as collected (while-alive estimand strategy) in addition to assuming participants who die prior to Day 29 to have met the endpoint (composite estimand strategy).

4.4.1.4. Total Intensive Care Length of Stay

A participant is defined as requiring intensive care if they received an intensive care unit in-patient healthcare encounter of any duration. A participant may have more than one period of intensive care stays included in the total intensive care length of stay.

Data will be summarised as collected (treatment policy estimand strategy) in addition to assuming participants who die prior to Day 29 to have been in intensive care from the date of death to Day 29 (composite estimand strategy).

4.4.1.5. SARS-CoV-2 Resistant Mutants Against VIR-7831 at Baseline

Summaries of viral resistance mutations at baseline will be provided based on frequency counts in the Safety analysis set.

4.4.1.6. Emergence of SARS-CoV-2 Resistant Mutants Against VIR-7831

Summaries of viral resistance mutations will be provided based on frequency counts in the Safety analysis set.

4.4.1.7. Reduction in SARS-CoV-2 Viral Load

Viral load will be log10-transformed prior to summary and analysis. The Virology analysis set will be used for all analyses.

Reduction of SARS-CoV-2 viral shedding will be determined by the change from baseline of SARS-CoV-2 nasal viral load at Day 3, Day 5, Day 11, Day 15, Day 22, and Day 29.

In addition, the SARS-CoV-2 viral load will also be assessed from the area under the curve (AUC as determined by the trapezoidal rule) of $\log_{10}$-transformed SARs-CoV-2 viral load through Days 1 to 5 ($AUC_{D1\text{-}5}$) and Days1 to 11 ($AUC_{D1\text{-}11}$). AUC will be log-transformed prior to analysis.

The proportion of participants with undetectable, unquantifiable and positive SARS-CoV-2 in nasal secretions by qRT-PCR at Day 3, Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29 will be summarised.

In addition a Kaplan-Meier plot of time to undetectable SARS-CoV-2 in nasal secretions by qRT-PCR by treatment group will be produced. For the purposes on the plot, a confirmed negative PCR is defined as first of two or more consecutive negative (no SARS-CoV2 detected) PCR tests.

4.4.1.8. SARS-CoV-2 viral load measured by qRT-PCR

Summaries will be provided to compare different sample collection methods in SARS-CoV-2 viral load (e.g. nasopharyngeal swab, saliva) within participants. The Virology analysis set will be used for all analyses.

4.4.1.9. SARS-CoV-2 anti-N antibody at Day 1 and Day 29

The incidence and titers (if applicable) of anti-N SARS CoV-2 antibodies at Day 1 and Day 29 will be summarized using frequency counts by treatment (including a total column) in the Safety analysis set.

4.4.1.10. Incidence and severity of Long COVID symptoms at Week 12, Week 24 and Week 36

To monitor for subsequent development of long COVID at Week 12, Week 24 and Week 36, participants will be asked a series of questions to evaluate a range of symptoms after first being infected with the SARS-CoV-2. The questions to be asked are defined in Appendix 6 of the Protocol.

The participant responses to the questions will be summarised, based on ITT analysis set. The frequency of the response Grade categories ("*Grade 1"* to "*Grade 3*") will be presented for each question.

4.4.2. Main Analytical Approach

All exploratory endpoints will be summarised only.

Total hospital length and total intensive care length of stay will only be summarised if at least 10% of participants have one or more recorded event of interest. Length of stay will be summarised in all patients in the analysis set, in addition to those with the event of interest. Otherwise the data will be listed only.

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

Subjects will receive either an IV infusion of sotrovimab or a single IM injection of sotrovimab at one of two dose levels.

The intravenous sotrovimab dose will be 500 mg and will be infused over 15 minutes. The intramuscular sotrovimab dose will be either 250 mg or 500 mg given at a single timepoint. The 250 mg IM dose will be given either as a single 250 mg (4ml) injection in the dorsogluteal muscle or as two 2 ml injections in each deltoid muscle. The 500 mg IM dose will be administered as two 4 ml injections in each dorsogluteal muscle.

Summaries of exposure will be limited to the number of participants exposed and the number of participants with interruptions or infusions/injections stopped early and not completed.

4.5.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards. As per the protocol, AEs are collected through Week 12 and SAEs collected through Week 36.

An overview summary of AEs will be produced, including counts and percentages of participants with:

- AEs
- AEs related to study intervention
- AEs leading to permanent discontinuation of study intervention,
- AEs leading to temporary interruption of study intervention
- Grade 3 and 4 AEs
- Grade 3 and 4 AEs related to study intervention,
- Grade 3 and 4 AEs leading to permanent discontinuation of study intervention,
- Grade 3 and 4 AEs leading to temporary interruption of study intervention
- SAEs
- SAEs related to study intervention,
- Fatal SAEs
- Fatal SAEs related to study intervention.
- Local infusion/injection site reactions

Adverse events will be coded using the latest version of the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the DAIDS 2017 v2.1.

The following adverse events will be considered of special interest (AESI) and will be summarised using frequency and percentages separately.

- Systemic infusion/injection related reactions (IRR) including hypersensitivity reactions (HSR); reactions within 24 hours of start of infusion will be identified using a list of MedDRA preferred terms confirmed by the Safety team.
- Local infusion/injection site reactions (ISR) will be identified using a list of MedDRA preferred terms confirmed by the Safety team.
- Immunogenicity (Anti-Drug Antibodies (ADA)) related adverse drug reactions will be reported. These potential events of ADAs will be detected by reviewing AEs that indicate HSR in those subjects who have positive anti-drug antibodies.
- Adverse events potentially related to antibody-dependent enhancement of disease (ADE) will be reported. These potential events of ADEs will be detected by reviewing adverse event/serious adverse events for an increase in the incidence and severity of COVID complications for a participant that cannot be explained by underlying risk factors.

In addition to the AE overview summary,

- Most common AEs defined as any AE preferred term (PT) with an incidence of at least ≥1% (approx. 2 subjects) in any of the treatment group will be summarised using frequency and percentages separately.
- AEs by severity will be presented. The summary will use the following algorithms for counting the participant:
    - Preferred term row: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
    - Any event row: Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

The frequency and percentage of AEs (all grades) will be summarized and displayed in descending order by system organ class (SOC) and PT.

In the SOC row, the number of participants with multiple events under the same SOC will be counted once.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible 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. The summary table will be displayed by PT only.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate listings will also be provided for study intervention-related SAEs.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing.

4.5.2.1. Disease-Related Events (not classified as AEs)

Disease-related events will be summarised by treatment group by overall frequency.

4.5.3. Laboratory Data

Summaries by shift tables of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DAIDS 2017 v2.1. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 2, any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0.

For laboratory tests with both low and high graded values, summaries will be provided separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

Any clinically abnormal laboratory results which are not identified as AEs will be summarised separately, identification of such values will be described in the OPS document.

For lab tests that are not gradable by DAIDS 2017 v2.1, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Summaries and listings for hematology, and chemistry laboratory tests will be produced separately. Liver function laboratory tests will be included with chemistry lab tests.

Separate summary of hepatobiliary laboratory events (if any) including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as elevated alanine aminotransferase (ALT) > 3×upper limit of normal (ULN), total bilirubin ≥ 2×ULN or international normalized ratio (INR) >1.5. Total bilirubin ≥ 2×ULN can be within 29 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin.

The summary will be produced for worst case post baseline only. A plot for maximum post-baseline Total Bilirubin against ALT will also be produced.

4.5.4. Vital Signs

Summaries of grade increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 2 and increase to Grade 3 for worst case post-baseline only. The grade definition for SBP is: Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3 (>=160). The grade definition for DBP is: Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3 (>=100). The summaries will be produced for worst case post baseline only.

In addition, summaries of respiratory rate, heart rate and temperature will be provided.

A boxplot will be presented for blood pressures by treatment. A summary of temperature will also be presented by planned visit/timepoints and pre-defined categories i.e., <38ºC, 38ºC-<38.4ºC, 38.4ºC-<38.9ºC, 38.9ºC-<40ºC and ≥40ºC.

In addition, listings of vital signs parameters (blood pressure, respiratory rate, heart rate and temperature) by visit will be provided.

4.5.5. Oxygen Saturation

Summaries of actual and changes in blood oxygen saturation (SpO_2) will be provided in addition a listing of participants administered oxygen.

Requirement for respiratory support is assessed according to the following categories:

1. Room air
2. Low flow nasal canulae/face mask
3. Non-re-breather mask or high flow nasal cannulae/ non-invasive ventilation (including continuous positive airway pressure support)
4. Mechanical ventilation / extra-corporeal membrane oxygenation
5. Other
6. Death

Changes in requirement for respiratory support (excluding room air) will be summarized using proportions of participants with change from baseline to higher respiratory support in each category by study day using a stacked bar chart.

4.6. Other Analyses

4.6.1. Subgroup analyses

The progression of COVID-19 through Day 29 will be summarised using counts and proportions for the following subgroups:

- Age (<65, ≥65 years)
- BMI (<30, ≥30kg/m^2)
- Duration of symptoms (≤5, >5 days)
- Sex (Female, Male)

Change from baseline in viral load will be summarised by visit in the following subgroups:

- Age (<65, ≥65 years)
- Baseline viral load (<4, ≥4-<5, ≥5-<6, ≥6-<7, ≥7 log_{10} copies/mL)
- Duration of symptoms (≤5, >5 days)
- Serological status (Positive, Negative)

4.7. Interim Analyses

The Joint Safety Review Team (JSRT) comprising individuals from Vir and GSK will

review safety data at regular intervals throughout the conduct of the study. Details of the JSRT process is recorded in relevant SRT documents.

A single interim analysis (IA) was initially planned to be performed for evaluation of safety, efficacy and futility when approximately 50% of participants are enrolled and reach Day 29. The IA data was to be evaluated by an IDMC. However, prior to the time of the planned analysis, the JSRT noted a discrepancy in the rate of progression to hospitalization occurring in the 250mg IM arm compared with the 500mg IM and IV arms. Upon review of the cumulative data, the JSRT made the decision to pause enrollment into the 250mg IM arm on 04-August-2021 and escalated the issue to the IDMC. An ad hoc meeting of the IDMC was called on 11-August-2021 and based upon their review of the data, the IDMC concurred that enrollment in the 250mg IM arm should be discontinued. As this ad hoc IDMC meeting occurred prior to the timepoint when the formal interim analysis would have occurred and concluded with discontinuing one arm of the study combined with an unexpected rapid increase in the rate of enrollment, it was not feasible to conduct the formal interim analysis.

There will be 2 reporting efforts: the primary Day 29 efficacy and safety analyses, and the 36-Week Safety Follow-Up analyses.

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 2.

Table 2 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Section 9.4.2: Planned primary endpoint model adjusted for treatment group, COVID-19 vaccination status, age (12-18, 19-64, ≥65 years old), region and gender.	• Planned primary endpoint model adjusted for treatment group, age (<65, ≥65 years old) and gender only.	• Model covariates amended due to small numbers of patients in non-US regions, small proportion of fully/partially vaccinated participants, and small number of participants <18 years.

5. SAMPLE SIZE DETERMINATION

Sotrovimab IM participants and sotrovimab IV participants were planned to be enrolled and randomized in a 1:1:1 ratio to receive a single dose IV infusion of sotrovimab or a single IM injection of sotrovimab at one of two dose levels, in an open-label manner.

Approximately 1020 (340 per arm) participants were planned to be randomly assigned to study intervention. This sample size will provide approximately 90% power to demonstrate that IM

injection of sotrovimab is non-inferior to IV infusion of sotrovimab in terms of the proportion of participants with progression of COVID-19 through Day 29 at the one-sided 2.5% significance level assuming COVID-19 progression rates of 2% in the sotrovimab IM and IV arms and 3.5% non-inferiority margin on the risk difference scale.

Following the discontinuation of sotrovimab 250 mg IM arm (See Section 4.7), no more participants were enrolled and randomized into this arm. The remaining participants were randomized in a 1:1 ratio to receive sotrovimab 500mg IV or sotrovimab 500 mg IM

Sample Size/Power Sensitivity

The table below shows power for showing non-inferiority for different true progression rates on the sotrovimab IV arm and when the progression rate in the sotrovimab 500mg IM arm is equal to or higher than that on IV, given a sample size of N=340 per arm.

		Progression rate in sotrovimab IV arm		
		1.0%	1.5%	2.0%
Progression rate in sotrovimab IM arm minus Progression rate in sotrovimab IV arm	0% (equal)	>99%	96%	90%
	+0.1%	99%	95%	88%
	+0.2%	98%	93%	85%
	+0.3%	97%	91%	82%

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Intent-to-Treat Analysis Set, unless otherwise specified. Please see Section 3 of the SAP for more information on analysis sets.

6.1.1. Participant Disposition

A summary of subject status and subject disposition for the study conclusion record will be provided. This display will show the number and percentage of subjects who completed the study and who withdrew from the study, including primary and secondary reasons for study withdrawal and presented in the order they are displayed on the collection form. A subject is

considered to have completed the study if he/she has completed the Week 36 visit. The end of the study is defined as the date of the last contact of the last subject in the study.

A summary of the number and percentage of subjects who passed screening and entered the study or who failed screening and therefore were not entered into the study, will be summarized along with the reasons for failure will be summarized for those subjects who failed screening. This summary will be produced based on the Screened analysis set.

The number of subjects will be summarized by Country, Site Id. and Investigator Id. This summary will be produced based on the Enrolled analysis set

A summary of the duration in days in follow-up since infusion/injection will be summarized categorically for the Safety analysis set. The duration is calculated using the following formula:

min (Date of study withdrawal, Date of Data Cut, Date of Study Completion) – Date of Dosing +1

where the earlier date of either a subject withdrawal from the study, the current data cut date, or the date a subject completed the study are used. The summary will display duration overall and by mortality status: alive or deceased. The study withdrawal date for deceased subjects coincides with their death date. Duration categories post-dose include:

- Less than 5 days
- 5 to 10 days
- 11 to 14 days
- 15 to 29 days
- Greater than 29 days
- Greater than 85 days
- Greater than 141 days
- Greater than 169 days
- Greater than 224 days

A summary of treatment exposure will display the number of subjects exposed, the duration of treatment administration, and the number of subjects with infusion/injection interrupted or stopped early and not completed using the Safety set.

A summary of the number of subjects in each of the analysis sets described in the SAP Section 3 will be provided. Also, a listing will display subject exclusions from any analysis set using the Screened analysis set.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age including age categories, race, ethnicity, sex, baseline height, baseline BMI and its categories) will be summarized by descriptive statistics. An

additional summary of age ranges using the EMA clinical trial results disclosure requirement categories will be produced and is based on the Enrolled analysis set (see SAP section 3).

The high-level FDA race categories and detailed race subcategories collected on the CRF will be summarized along with categories for mixed race based on the Intent-to-treat analysis set.

Number of positive SARS-CoV-2 results, specimen type used for SARS-CoV-2 test, diagnostic method, risk factors for COVID-19 progression (as listed in the Protocol Inclusion Criteria), number of COVID-19 conditions met, types of symptoms present, and symptom duration will be summarized.

Additionally, the Baseline Disease Characteristics table will summarize subjects with a baseline obesity risk factor as (BMI $\geq$30kg/m^2 for adult participants and BMI $\geq$85th percentile for age/gender based on CDC growth charts for adolescents) and summarize COPD risk factor to include the following protocol-defined conditions: history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion.

The summary of stratification factors will be provided:

- Age: 12-17 years old, 18-64 years old, and $\geq$65 years old.
- COVID-19 Vaccination History: receipt of any COVID-19 vaccine.
- Region of the world (Europe, North America, South America, South Asia, Rest of Asia, Rest of the World).

Medical conditions collected at screening will be summarized separately by past and current. These factors will be summarized as collected for current medical conditions at screening.

6.1.3. Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized. 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.

Data will be reviewed prior to unblinding and freezing the final Day 29 efficacy database to ensure all important deviations are captured and categorized in the protocol deviations SDTM dataset.

6.1.4. Prior and 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. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Anatomical Therapeutic Chemical (ATC) Level 1 (Body System) and by Ingredient. Standard of care concomitant medications taken for COVID-19 will also be summarized. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Concomitant Medications will be summarized and listed, while prior medications will be listed.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

This study will not be utilizing lab parameter ranges defining potential clinical important values.

Instead, summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DAIDS 2017 v2.1, if available.

6.2.2. Laboratory Values with DAIDS 2017 v 2.1 Grading

Laboratory parameters of interest	Grade			
	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
Absolute Neutrophil Count (ANC), Low (cells/mm3; cells/L) > 7 days of age	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
Absolute Lymphocyte Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	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
WBC, Decreased (cells/mm3; cells/L) > 7 days of age	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

Hemoglobin16, Low (g/dL; mmol/L) ≥ 13 years of age (male only)	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
Hemoglobin16, Low (g/dL; mmol/L) ≥ 13 years of age (female only)	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
Platelets, Decreased (cells/mm3; cells/L)	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 x10^9
INR, High (not on anticoagulation therapy)	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
ALT or SGPT, High Report only one	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
AST or SGOT, High Report only one	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
Total Bilirubin, High > 28 days of age	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
Potassium, High (mEq/L; mmol/L)	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)	3.0 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
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x subject's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x subject's baseline	≥ 3.5 x ULN OR Increase ≥ 2.0 x subject's baseline
Creatinine Clearance or eGFR, Low *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from subject's baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR 30 to < 50% decrease from subject's baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from subject's baseline or dialysis needed

Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory

6.2.3. Study Period

Study phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is prior treatment start, or if end date is missing but the medication end reference equals BEFORE.
Concomitant	Any medication that is not a prior

Study Treatment Emergent Flag for Adverse Event

Flag	Definition
Study Treatment Emergent	If AE onset date is on or after study treatment start date: • Study Treatment Start Date ≤ AE Start Date

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.
- All Adverse Events tables and figures will be presented for Treatment Emergent AEs. AE listings will display all data.

6.2.4. Study Day and Reference Dates

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

For efficacy, measurements of progressions including: all Hospitalizations, Oxygen Supplementation, and Death will measure from treatment start date to align with safety measurements. Efficacy measurements of all-cause mortality and incidence & duration of ICU, Hospitalization, and Ventilation will calculate study day from date of randomization.

- Ref Date = Missing → Study Day = Missing
- Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
- Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

6.2.5. Multiple measurements at One Analysis Time Point

Where duplicate records exist per scheduled visit/time point/participant (if applicable) in vital signs (including oxygen saturation), laboratory data, and ECG measurements the latest record will be used for summaries.

Subjects having both High and Low values for DAIDS 2017 v2.1 or Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance (PCI) summary tables where instead of PCI ranges DAIDS 2017 v2.1 or Normal ranges will be considered for reporting of clinically important safety findings.

All data from scheduled and unscheduled visits will be reported in the listings.

6.2.6. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the listing. o Answers such as "Not applicable", "Not evaluable" and "Not Done" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Efficacy Endpoints	Details around the missing data handling for efficacy endpoints are described in section 6.2.8. In addition: • For the secondary binary endpoint of proportion of subjects who have progression of COVID-19 (i.e., hospitalisation (any duration) OR emergency room visit OR death) through Day 29, missing data will be handled as for the primary endpoint.
Safety Endpoints	• No missing data imputation will be performed for safety endpoints. • Data will be reported as captured.

6.2.7. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject 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.

<table>
<tr><th>Element</th><th>Reporting Detail</th></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 treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.
Else if study treatment start date is not missing:

If month and year of start date = month and year of study treatment start date, then

If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.
Else set start date = study treatment start date.

Else set start date = 1st of month.

</td></tr>
<tr><td>Missing start day and month</td><td>

If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.
Else if study treatment start date is not missing:

If year of start date = year of study treatment start date, then

If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.
Else set start date = study treatment 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</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 treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.
Else if study treatment start date is not missing:

If month and year of start date = month and year of study treatment start date, then

If stop date contains a full date and stop date is earlier than study

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

Element	Reporting Detail		
		treatment start date, then set start date= 1st of month. ▪ Else set start date = study treatment start date. • Else set start date = 1st of month.	
	Missing start day and month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date, then ▪ If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1. ▪ Else set start date = study treatment 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	
Oxygen Supplementation	Completely missing end date	If the end date is missing and subsequent record exists and is not missing the start date, impute the missing end date as the start date of the subsequent record. If end date is missing and no subsequent record exists, the method of oxygen supplementation will be considered ongoing at time of database extraction.	
Age	Age will be imputed from year of birth. The calculation will use 30 June as the day and month and will calculate the age relative to Screening date.		

6.2.8. Statistical Modelling - Multiple Imputation

Multiple imputation will be used to impute data that is missing following withdrawal of the subject from the study, or following an intercurrent event for hypothetical estimands (if applicable), for the following two binary endpoints:

- Progression of COVID-19 through Day 29 as defined by hospitalization > 24 hours for acute management of illness due to any cause or death

- Progression of COVID-19 through Day 29 as defined by visit to a hospital emergency room for management of illness or hospitalization for acute management of illness for any duration and for any cause or death

Multiple imputation of endpoint data will be performed to impute data post study withdrawal or intercurrent event, as follows:

- Data will have a monotone missing structure so there will be no intermittent missing data.
- Imputation of missing data will proceed iteratively for each study day starting with Day 2 and ending at Day 29 using a logistic regression imputation model including the analysis model covariates and a parameter for COVID-19 progression status for the previous study day, i.e. imputation of COVID-19 progression status at Day X will include a covariate for status at Day X-1 from the previous imputation step.
- The "likelihood=augment" option in PROC MI will be used in the imputation to avoid quasi complete separation of data for the preceding timepoint covariate included in the imputation model. If logistic regression step fails to converge the following back-up options may be used:
    i) A discriminant function [Brand, 1999] may be used in place of logistic.
    ii) MCMC with adaptive rounding.

A sufficient number of imputations will be performed to ensure the stability of the estimates. The results of analysis from each complete imputed dataset will be combined using Rubin's rule.

Table 3 Multiple Imputation Specifications) details the models, covariates and the seed to be used for the analyses.

Table 3 Multiple Imputation Specifications

Endpoint	Model	Covariates	Post-Baseline Timepoints Included in Prediction Model for Day X (X=2,…,29)	Initial Seed
Proportion of participants who have progression of COVID-19 at Day 29 (hospitalized >24h/death)	Monotone Binary Logistic Regression	Treatment, Age Group at Baseline, Sex	Day X-1	6862
Proportion of participants who have progression of COVID-19 at Day 29 (ER visit/hospitalized/death)	Monotone Binary Logistic Regression	Treatment, Age Group at Baseline, Sex	Day X-1	376

The seeds were generated using the following code:

```
DATA seeds;
DO i=1 to 3;
seed=int(10000*ranuni(214366));
```

```
OUTPUT;
END;
RUN;
```

The same seed is used for all estimands and sensitivity analyses. If additional seeds are required, then the initial seed as specified will be incremented by 1.

6.2.9. Count Data Model Checking

Distributional assumptions underlying the model used for analysis will be checked. If there are any departures from the distributional assumptions, alternative models may be explored.

6.2.10. Continuous Data Model Checking

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.

If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

6.2.11. Early PK Access Key Activities

PK dummy activities will be performed as per the standard process. The details of dummy activities will be explained in the OPS

6.2.12. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
None

7. REFERENCES

Brand, J. P. L. Development, Implementation, and Evaluation of Multiple Imputation Strategies for the Statistical Analysis of Incomplete Data Sets. Ph.D. thesis, Erasmus University 1999.

Carpenter, J.R. & Kenward M.G. Multiple Imputation and its Applications. Wiley 2012.