Statistical Analysis Plan (SAP)

Study ID: 215226

Official Title of Study: An open-label, non-comparator, multicenter study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous or intramuscular dose of sotrovimab in pediatric participants with mild to moderate COVID-19 at high risk of disease progression

NCT number: NCT05124210

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TITLE PAGE

Protocol Title: An open-label, non-comparator, multicenter study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous or intramuscular dose of sotrovimab in pediatric participants with mild to moderate COVID-19 at high risk of disease progression

Study Number: 215226 (VIR-7831-5005)

Compound Number: GSK4182136 (VIR-7831; sotrovimab)

Abbreviated Title: Pharmacokinetics, pharmacodynamics, and safety of single-dose sotrovimab in high-risk pediatric participants with mild to moderate COVID-19

Acronym: COMET-PACE **(CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial- **P**edi**A**tri**C** **E**arly treatment)

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	10 Feb 2022	Amendment 1 (01-October-2021)	Not Applicable	Original version
2.0	30 Jun 2023	Amendment 1 (01-October-2021)	To include further analyses of viral mutations and viral load.	Further analysis request for resistant mutants exploratory endpoint incorporating viral load.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses for study 215226.

This SAP covers the analyses planned for the following deliverables: the in-stream IDMC reviews [including the Day 29 PK and safety reporting of Cohort A (12 to <18)], Cohort A Day 29 Statistical Analysis Complete (SAC), Cohort B Day 29 SAC, and Cohort A and Cohort B final Week 36 SAC. Note that if required, the Cohort A and Cohort B final Week 36 SAC may be reported as two separate SACs i.e. the Cohort A Week 36 SAC and the Cohort B Week 36 SAC. Details of the planned analyses are provided in Section 4.7 and Section 4.8. The OPS covers specific analysis for each deliverable.

Data from each cohort of the study will be reported separately. In addition, the Week 36 analysis will cover Day 29 endpoints if Day 29 SACs have not been reported, by using study day to flag the data for endpoints through Day 29.

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.

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

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the pharmacokinetics by IV or IM administration of sotrovimab in children from birth to <18 years	• Body weight-adjusted serum clearance of sotrovimab • Serum PK of sotrovimab administered by IM injection or IV infusion (PK parameters may include C_{max}, T_{max}, AUC_{inf}, $t_{1/2}$, V_z, CL, F)
To evaluate the safety and tolerability of sotrovimab by IV or IM administration	• Incidence of adverse events (AEs) through Day 29 and Week 36 • Incidence of serious adverse events (SAEs) through Day 29 and Week 36 • Incidence of adverse events of special interest (AESI) through Day 29 and Week 36

Objectives	Endpoints
Secondary	
To evaluate disease progression following IV or IM administration of sotrovimab	• Progression of COVID-19 through Day 29 as defined by need for attended medical visit* or escalation to higher level of medical care or death *An attended medical visit includes visit to a hospital emergency room for management of illness or hospitalization for acute management of illness • Development of severe and/or critical respiratory COVID-19 as manifested by requirement for supplemental oxygen through Day 29* *For participants who require oxygen or respiratory support for premorbid conditions, disease progression is defined as any sustained (>24 hours) increase in the level or method of oxygen support required
To characterize the effect of IV or IM administration of sotrovimab on SARS-CoV-2 viral load in respiratory tract samples among participants infected with SARS-CoV-2	• Change from baseline in viral load in nasal secretions measured by qRT-PCR at Day 5, Day 8, and Day 11

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1.1.2. Estimands

Each study objective is presented in Table 1 with additional information, including prespecified estimands with related attributes.

Table 1 Estimands

Objective	Objective Category	Estimand				
		Variables/Endpoints[a]	Analysis Set	Intercurrent Event Strategy		Summary Measure
				Event	Strategy	
To evaluate the pharmacokinetics by IV or IM administration of sotrovimab in children from birth to <18 years	Primary	• Body weight-adjusted serum clearance of sotrovimab	PK Principal Stratum[b]	- Participants receiving incomplete IV/IM dose	Principal Stratum Strategy, where we are only interested in the strata of participants who would be able to receive a complete IV/IM dose.	PK model parameters (except for the Cohort A (12 to <18 years) Day 29 in-stream review where non-compartmental analysis (NCA) will be used)
		• Serum PK of sotrovimab administered by IM injection or IV infusion (PK parameters may include C_{max}, T_{max}, AUC_{inf}, $t_{1/2}$, V_z, CL, F)	PK Principal Stratum[b]	- Participants receiving incomplete IV/IM dose	Principal Stratum Strategy, where we are only interested in the strata of participants who would be able to receive a complete IV/IM dose.	

Objective	**Objective Category**	**Estimand**				
		Variables/Endpoints[a]	**Analysis Set**	**Intercurrent Event Strategy**		**Summary Measure**
				Event	**Strategy**	
To evaluate the safety and tolerability of sotrovimab by IV or IM administration	Primary	• Incidence of adverse events (AEs) through Day 29 and Week 36	Safety	- Participants receiving incomplete IV/IM dose - Use of non-permitted medications	Treatment Policy Strategy, where data after the intercurrent event will be included.	Counts and percentages
		• Incidence of serious adverse events (SAEs) through Day 29 and Week 36	Safety	- Participants receiving incomplete IV/IM dose - Use of non-permitted medications	Treatment Policy Strategy, where data after the intercurrent event will be included.	
		• Incidence of adverse events of special interest (AESIs) through Day 29 and Week 36	Safety	- Participants receiving incomplete IV/IM dose - Use of non-permitted medications	Treatment Policy Strategy, where data after the intercurrent event will be included.	

Objective	**Objective Category**	**Estimand**				
		Variables/Endpoints[a]	**Analysis Set**	**Intercurrent Event Strategy**		**Summary Measure**
				Event	**Strategy**	
To evaluate disease progression following IV or IM administration of sotrovimab	Secondary	• Progression of COVID-19 through Day 29 as defined by need for attended medical visit* or escalation to higher level of medical care or death *An attended medical visit includes visit to a hospital emergency room for management of illness or hospitalization for acute management of illness	Safety	- Participants receiving incomplete IV/IM dose - Use of non-permitted medications	Treatment Policy Strategy, where data after the intercurrent event will be included.	Counts and percentages

Objective	Objective Category	Estimand				
		Variables/Endpoints[a]	Analysis Set	Intercurrent Event Strategy		Summary Measure
				Event	Strategy	
		• Development of severe and/or critical respiratory COVID-19 as manifested by requirement for supplemental oxygen through Day 29* *For participants who require oxygen or respiratory support for premorbid conditions, disease progression is defined as any sustained (>24 hours) increase in the level or method of oxygen support required	Safety	- Participants receiving incomplete IV/IM dose - Use of non-permitted medications - Death	Treatment Policy Strategy, (for the intercurrent events of participants receiving incomplete IV/IM dose and use of non-permitted medications), where data after the intercurrent event will be included. Composite Strategy (for the intercurrent event of death), where participants who die (due to any cause) prior to the timepoint of interest without first having received supplemental oxygen will be considered to have met the endpoint.	Counts and percentages

Objective	Objective Category	Estimand				
		Variables/Endpoints[a]	Analysis Set	Intercurrent Event Strategy		Summary Measure
				Event	Strategy	
To characterize the effect of IV or IM administration of sotrovimab on SARS-CoV-2 viral load in respiratory tract samples among participants infected with SARS-CoV-2	Secondary	• Change from baseline in viral load in nasal secretions measured by qRT-PCR at Day 5, Day 8, and Day 11	Virology	- Participants receiving incomplete IV/IM dose - Use of non-permitted medications	Treatment Policy Strategy, where data after the intercurrent event will be included.	Descriptive Statistics (including n, mean, standard deviation etc)
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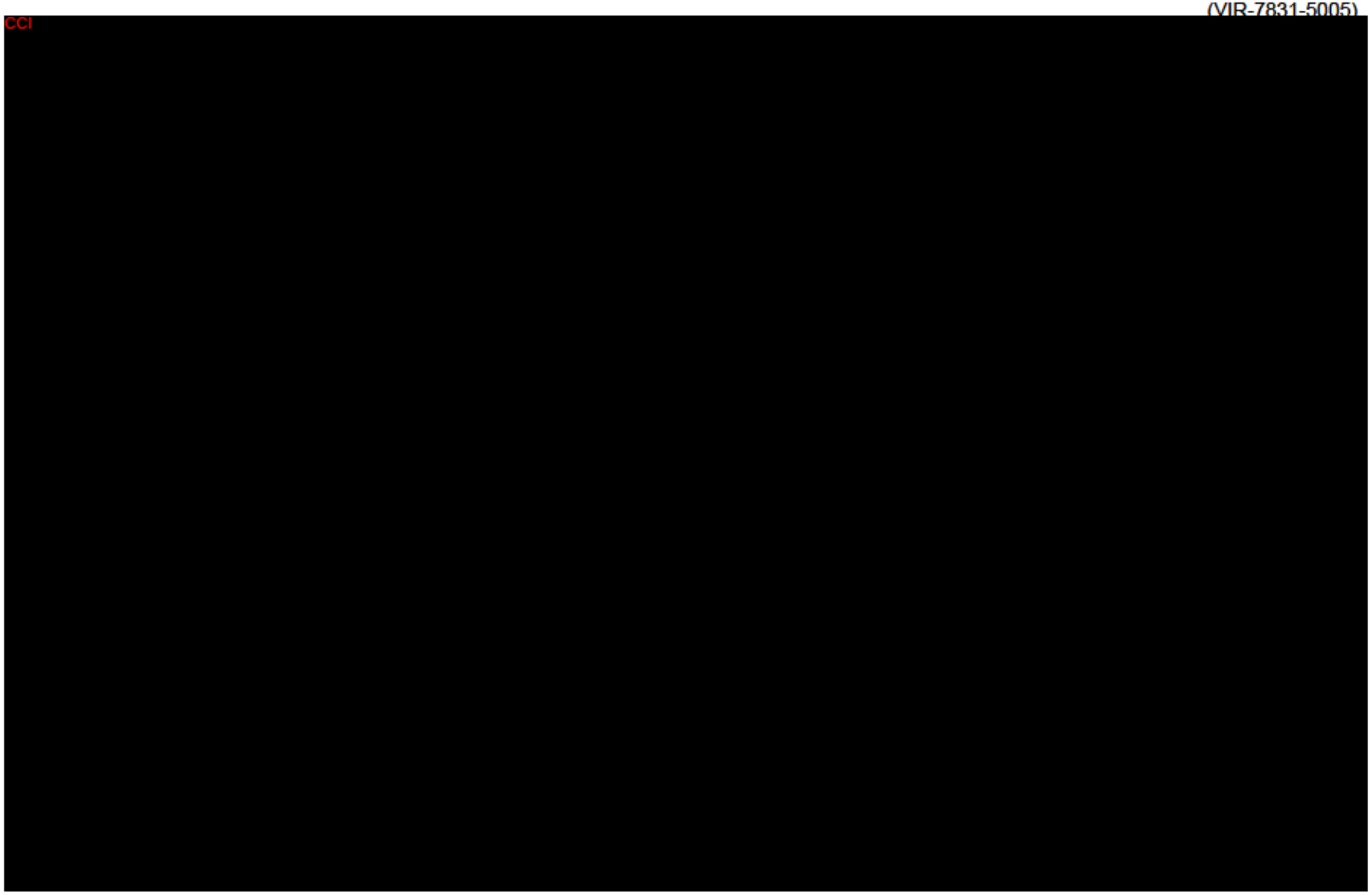
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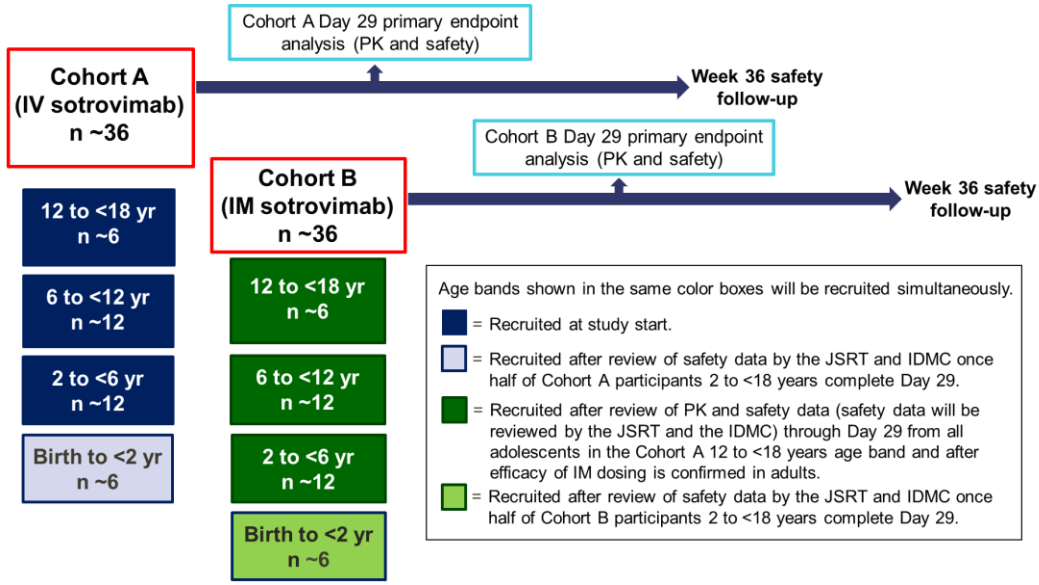
Abbreviations: ADA = anti-drug antibodies; AEs = adverse events; AESI = adverse events of special interest; CCI AUC$_{inf}$ = area under the serum concentration-time curve from time zero to infinity; C$_{max}$ = maximum observed concentration; CL = clearance; ECGs =electrocardiograms; F = bioavailability; IM = intramuscular; IV = intravenous; PK = pharmacokinetics; SAEs = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; $t_{1/2}$ = terminal elimination half-life; T$_{max}$ = time to reach C$_{max}$; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction; V_z = apparent volume of distribution during terminal phase.
[a] Endpoints will be assessed separately for IV and IM treatment. [b] Refer to Section 3 for the definition of the PK Stratum analysis set.

1.2. Study Design

Overview of Study Design and Key Features



Abbreviations: IDMC = Independent Data Monitoring Committee IM = intramuscular; IV = intravenous; JSRT = Joint Safety Review Team; n = number of participants enrolled; PK = pharmacokinetics; yr=years.

Design Features

- This study is a Phase 2b open-label, non-comparator, multi-center study to evaluate PK, safety, and PD of IM or IV administration of sotrovimab in pediatric participants aged from birth to <18 years with mild/moderate COVID-19 at high risk of disease progression.
- This study includes 2 cohorts (Cohort A and Cohort B). Participants in Cohort A will receive IV sotrovimab and participants in Cohort B will receive sotrovimab via IM injections.
- Cohort A and Cohort B will each enroll approximately 36 participants; therefore, a total of approximately 72 participants will be enrolled in this study. Four age bands are planned to be enrolled in this this study. The following number of participants will be enrolled in each age band for each Cohort:
  - Adolescents aged 12 to less than 18 years: approximately 6 participants
  - Children aged 6 to less than 12 years: approximately 12 participants
  - Children aged 2 to less than 6 years: approximately 12 participants
  - Birth to less than 2 years: approximately 6 participants
- Recruitment will start with Cohort A as follows:
  - The Cohort A 2 to <18 years age bands will be recruited simultaneously.
  - The Cohort A birth to <2 years age band will be recruited if deemed appropriate by the JSRT and IDMC after review of safety data once half of Cohort A participants 2 to <18 years (i.e., 15 participants) complete Day 29.

  Recruitment in Cohort B will occur as follows:

Overview of Study Design and Key Features

- Cohort B will start recruitment if deemed appropriate after review of PK data through Day 29 from all adolescents in the Cohort A 12 to <18 years age band (i.e., 6 participants) and after the efficacy of IM dosing is confirmed in adults. Safety data through Day 29 from all Cohort A 12 to <18 years age band participants will also be reviewed by the JSRT and the IDMC prior to initiating Cohort B recruitment. Following favorable review, the Cohort B 2 to <18 years age bands will be recruited simultaneously.
- The Cohort B birth to <2 years age band will be recruited if deemed appropriate by the JSRT and IDMC after review of safety data once half of Cohort B participants 2 to <18 years (i.e., 15 participants) complete Day 29.

- All participants in Cohort A and Cohort B will be actively monitored on an outpatient basis through 36 weeks after dosing (Week 36) with frequent collection of nasal mid-turbinate swabs for virology and resistance analyses. Participants will have blood draws for PK sampling, anti-drug antibodies (ADA) testing, and for safety assessments; participants will have other in-clinic or home evaluations as detailed in the Schedule of Activities. Additionally, all participants ≥2 years of age will have blood draws for assessment of anti-nucleocapsid (anti-N) and anti-spike (anti-S) SARS-CoV-2 antibodies.
- After IV infusion or IM injection, participants will be monitored for 2 hours. Local injection site tolerability will also be monitored during the 2 hours post-dose. Throughout the study, a JSRT and IDMC will review safety data from all participants enrolled in either Cohort. After half of participants are dosed in either Cohort (Cohort A or Cohort B), the JSRT will review safety data and, if there are no safety concerns, a recommendation may be made by the JSRT to reduce the post-dose Day 1 monitoring and observation time to 1 hour within the same Cohort.
- COVID-19 disease progression will be monitored daily from Day 1 through Day 14 by a phone call on days when a home visit or clinic visit is not scheduled. COVID-19 disease progression will also be monitored on Day 22 and Day 29. Additionally, a weekly phone call will be conducted starting at Week 5 on weeks when there is not a scheduled clinic/home visit. Participants will be followed for a period of 36 weeks from dosing.

Study treatment

- Dosing will be based on weight in each age band as follows:

Age	Weight Band	Dose (mg)	Volume (mL)
0 to <2 years	2 to <5 kg	62.5	1
	5 to <15 kg	125	2
	15 to <40 kg	250	4
2 to <6 years	5 to <15 kg	125	2
	15 to <40 kg	250	4

Overview of Study Design and Key Features	
	<table><tr><td>6 to <12 years</td><td>15 to <40 kg ≥40 kg</td><td>250 500</td><td>4 8</td></tr><tr><td>12 to <18 years</td><td>15 to <40 kg ≥40 kg</td><td>250 500</td><td>4 8</td></tr></table> Intravenous sotrovimab will be administered undiluted using a syringe pump for participants under <15 kg and diluted in 40 mL saline for participants ≥15 kg. Intramuscular injections will be administered without any saline dilution. • All participants will receive Standard of Care (SoC) as per institutional protocols, in addition to the study treatment.
Study treatment Assignment	• The decision to enroll participants in Cohort A or Cohort B will be per investigator discretion when both Cohorts enroll a given age group simultaneously. By using the Interactive Response Technology (IRT) system, the dispensation will be monitored to ensure that the target number of participants in each Cohort and in each age band will receive IV infusion or IM injection. • Participants will receive sotrovimab directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. When multiple IM injections are performed, the time recorded should be the first injection. The infusion start and stop times will be recorded for IV administration.
Interim Analysis	• An IDMC will review safety and PK (where applicable) data throughout the conduct of the study at regular intervals. Details of the planned reviews are included in Section 4.7 of this SAP. • The Joint Safety Review Team (JSRT) comprising individuals from Vir and GSK will review safety and PK data (where applicable) at regular intervals throughout the conduct of the study. Details of the JSRT process is recorded in relevant SRT documents. Details of the planned reviews are included in Section 4.7 of this SAP.

2. STATISTICAL HYPOTHESES

The primary objectives are the assessment of the PK and safety of single-dose sotrovimab administered via IV infusion (Cohort A) or IM injection (Cohort B) in pediatric participants aged from birth to <18 years with mild/moderate COVID-19 at high risk of disease progression. There are no formal statistical hypotheses associated with these objectives and no formal significance tests will be performed.

2.1. Multiplicity Adjustment

No multiplicity adjustment is planned for this study.

3. ANALYSIS SETS

The analysis sets described in this section will be defined separately for Cohorts A and Cohort B.

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened (Cohort A/Cohort B)	All participants who were screened for eligibility	Study Population
Enrolled (Cohort A/Cohort B)	All participants who entered the study. Note, participants who were assigned a randomisation ID are considered enrolled. Note screening failures (who never passed screening) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Safety (Cohort A/Cohort B)	All participants who are exposed to study treatment. Participants will be analyzed according to the treatment they actually received.	Study Population Safety Virology
Pharmacokinetic (PK) (Cohort A/Cohort B)	All participants who are exposed to study treatment and who had at least 1 non-missing PK assessment (non-quantifiable [NQ] values will be considered as non-missing values). Data will be reported according to the treatment they actually received.	PK
Virology (Cohort A/Cohort B)	All participants who are exposed to study treatment and have a quantifiable SARS-CoV-2 viral load measurement at baseline. Data will be reported according to the treatment they actually received.	Virology
PK Principal Stratum (Cohort A/Cohort B)	All participants in the PK analysis set who would be able to complete the IV/IM dose. Participants will be analyzed according to the treatment they actually received.	PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Unless otherwise specified, the Safety analysis set will be used for all Study Population and Safety analyses. The PK Principal Stratum analysis set will be used for all PK analyses and the Virology analysis set will be used for all Virology analyses.

The treatment display format to be used in the planned outputs will be specified in OPS.

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 also present the geometric mean and coefficient of variation for data that is transformed back to the original scale. Categorical data will be summarized as the number and percentage of participants in each category.

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

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. The only exception will be summary tables displaying the number of participants by country and site (see OPS for further details).

4.1.2. Baseline and Post-Baseline Definition

For all endpoints (except for ECGs and respiratory status) 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 ECGs, triplicate 12-lead ECGs are collected at screening and the average of the three measurements will be used as the baseline value. Note, only the triplicate ECGs collected at screening will be used as the baseline value; i.e., if a participant also has a single pre-dose ECG reading collected on Day 1, this Day 1 pre-dose ECG will not be included as the baseline value. If only a single pre-dose ECG is available (i.e. no triplicate was done) then this will be used as the baseline value.

For respiratory status, the status recorded at Day 1 will be used as the baseline status.

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 Endpoints Analyses

4.2.1. Pharmacokinetics (PK)

4.2.1.1. Definition of Endpoints

The primary PK endpoints are:

- Body weight-adjusted serum clearance of sotrovimab.
- Serum PK of sotrovimab administered by IM injection or IV infusion.

Serum pharmacokinetic parameters will be calculated using non-compartmental analysis (NCA) for the planned Day 29 in-stream review(s) (see Section 4.7). The full Day 29 analysis of Cohorts A and B, as well as the end of study analysis will report parameters predicted using population PK modelling approaches according to current Clinical Pharmacology Modelling & Simulation (CPMS) working practices and using the currently supported version of NONMEM, R, SAS, or equivalent software. PK parameters for the planned Day 29 in-stream review(s) will be calculated using Phoenix WinNonlin or R.

Calculations of pharmacokinetic parameters for all PK analyses will be based on actual sampling times. Pharmacokinetic parameters listed 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_{inf}	Area under the concentration-time curve from time 0 to infinity.
$\%AUC_{exp}$	The percentage of AUCinf obtained by back-extrapolation
$AUC_{D1\text{-}29}$	Area under the concentration-time curve from Day 1 predose to Day 29.
$AUC_{D1\text{-}last}$	Area under the concentration-time curve from Day 1 predose to Day Last
C_{D29}	Observed Serum concentration on Day 29
C_{last}	Last measurable serum concentration
CL	Apparent total body clearance of the drug from serum
C_{max}	Maximum observed serum concentration, determined directly from the concentration-time data.
T_{max}	Time to reach Cmax, determined directly from the concentration-time data

$t_{½}$	Apparent terminal phase half-life will be calculated as: $t½ = \ln 2 / \lambda z$
T_{last}	Time of the last quantifiable concentration
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.

For the planned Day 29 in-stream review(s), only C_{max}, T_{max}, $AUC_{D1\text{-}29}$, and C_{D29} will be reported. In the case of a safety signal with neonates or infants, other parameters (e.g. $AUC_{0\text{-}inf}$) will also be provided for the in-stream review(s).

4.2.1.2. Main Analytical Approach

The primary pharmacokinetic analyses will be based on the PK Principal Stratum analysis set, unless otherwise specified. The estimands are described in Table 1. Missing data will not be imputed.

All PK listings will be based on the PK analysis set, unless otherwise specified.

Drug Concentration Measures

Concentrations of sotrovimab in serum through Day 29 and through Week 12 will be listed for all participants by actual time and summarised by nominal time, for the Day 29 SACs [including the Day 29 PK and safety reporting of the planned Day 29 in-stream review(s) and the Week 36 SAC, respectively. Standard summary statistics will also be calculated (i.e. n, geometric mean, arithmetic mean, standard deviation, median, minimum and maximum). For more information regarding the handling of serum concentrations below the assay's lower limit of quantification (BLOQ), refer to Appendix 3, which is based on GSK R&D Guideline: CCI [redacted] CCI [redacted]

Individual serum concentration-time profiles, median profiles and mean profiles will be plotted for each participant 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.

Derived PK Parameters for the Day 29 In-Stream Review(s)

The PK parameters will be summarised as described below. Individual participant PK parameter values will also be listed. 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: $T_{max,}$	n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum
Log_e-transformed Data: AUC_{D1-29}, C_{last}, C_{max}	n, geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and $\%CV_b$ (percent coefficient of variation between groups)

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

Derived PK Model Parameters Using Population PK Analyses

Concentrations from the PK samples collected in this study will be analysed by population PK methods. Population PK analysis will be performed by CPMS. This will be the subject of a separate analysis plan.

4.2.2. Safety

4.2.2.1. Definition of Endpoints

The primary safety endpoints are:

- Incidence of AEs through Day 29 and Week 36.
- Incidence of SAEs through Day 29 and Week 36.
- Incidence of AESIs through Day 29 and Week 36.

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. The estimands are described in Table 1. Missing data will not be imputed.

Incidence of AEs, SAEs, and AESIs through Day 29 and through Week 36 will be displayed in the form of summaries, listings, and figures (where appropriate) for the respective deliverables i.e. in-stream IDMC reviews, Cohort A Day 29 SAC, Cohort B Day 29 SAC and/or Cohort A and B Week 36 SAC. Note, study day will be used to flag safety data through Day 29 for the safety endpoints through Day 29. For endpoints through Week 36, all safety data available in the database at the time of reporting the deliverable of interest will be used

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 Corrected v2.1.

Adverse Events

An overall summary of safety criteria (as defined in the OPS) will be produced, including counts and percentages of participants with all-cause mortality, any SAE, renal events, cardiac events, pulmonary events and any disease related events.

An overview summary of AEs will be produced, including counts and percentages of participants with any AE and any SAEs.

In addition, the number and percentage of participants with AEs, drug-related AEs, SAEs and drug-related SAEs will be summarised in separate tables by System Order Class (SOC), Preferred Term (PT) and Maximum Grade. Participants who experienced the same event several times with different grades will only be counted once with the maximum grade.

The number and percentage of participants with AEs leading to discontinuation of study treatment, AEs leading to study withdrawal and AEs leading to interruption of study treatment will also be summarised in separate tables by SOC and PT. A separate summary by SOC and PT of SAEs (number of participants and occurrences) and a separate summary of common (≥ 5% in total arm [across all age bands] within a cohort) non-serious AEs (number of participants and occurrences), will also be provided.

The number and percentage of participants with non-serious drug-related AEs and serious fatal and non-fatal drug-related AEs will also be provided in separate tables summarised by PT only.

The frequency and percentages will be summarized and displayed in descending order by SOC and PT (as applicable).

A drug-related AE is defined as an AE for which the investigator classifies the possible relationship to study treatment as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. if the relationship to study treatment is missing, the event will be considered drug-related.

Listings of AEs (including participant numbers for individual treatment emergent AEs, all AEs, fatal SAEs, non-fatal SAEs, AEs leading to permanent discontinuation of study treatment or withdrawal from study, AEs leading to interruption of study treatment, and reasons for considering as an SAE) will also be provided.

Adverse Events of Special Interest

The following adverse events will be considered of special interest (AESI):

- Hypersensitivity reactions (HSRs); these are events reported at any time post dose and pooled using Hypersensitivity SMQ narrow terms (minus few terms specific local injection site reaction to avoid duplication with ISRs). These will be identified using a list of MedDRA preferred terms confirmed by the Safety team.

- Infusion related reactions (IRR) including hypersensitivity reactions (HSR) and anaphylaxis; reactions within 24 hours of start of infusion will be identified using a list of MedDRA preferred terms confirmed by the Safety team. Note this AESI is only applicable to those participants that are on Cohort A (IV).
- Injection site reactions (ISR) will be identified using a list of MedDRA preferred terms under MedDRA Injection site reaction HLT. Note this AESI is only applicable to those participants that are on Cohort B (IM).
- Immunogenicity (Anti-Drug Antibodies [ADA]) related adverse events will be reported after the end of the Week 36 reporting period and included in the CSR.
- Adverse events potentially related to antibody-dependent enhancement of disease (ADE) will be reported after the end of the Day 29/Week 36 reporting periods and included in the respective CSRs. As part of the Day 29/Week 36 reporting, a listing of cardiac events of interest and a listing of eGFR and UACR for participants with a renal event of interest will be produced. Pulmonary event outputs including baseline and post-baseline respiratory status will also be produced. Additional summaries of pulmonary and COVID related events may also be produced post-SAC if required. The safety team will review these outputs together with various AE data from the study in order to identify these events.

For the AESIs of HSRs, IRRs and ISRs, the number and percentages of participants with the event will be summarized by PT, unless otherwise specified in the OPS. In addition, a summary of characteristics table and a summary of onset and duration of the first occurrence table will be provided separately for each of these AESI groups. A separate listing of participant numbers for each of these AESI groups will also be produced. A comprehensive list, including the MedDRA terms which contribute to each of these AESI groups will be used for each AESI group. It will be based on the current MedDRA version and the safety review team (SRT) agreements in place at the time of reporting where applicable. This will be finalized prior to unblinding.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of Endpoints

4.3.1.1. Progression of COVID-19 through Day 29

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

1. Need for attended medical visit – i.e., visit to a hospital emergency room or hospitalization for management of illness for any duration and for any cause **OR**
2. Escalation to higher level of medical care **OR**
3. Death (due to any cause)

4.3.1.2. Development of Severe and/or Critical Respiratory COVID-19 through Day 29

Participants are defined as developing severe and/or critical respiratory COVID-19 if they require use of supplemental oxygen through Day 29. For participants who require

oxygen or respiratory support for premorbid conditions, disease progression is defined as any sustained (>24 hours) increase in the level or method of oxygen support required at any point through Day 29. This will be as collected in the eCRF.

Participants who die (due to any cause) prior to the timepoint of interest without first having met the endpoint will be considered to have met the endpoint (composite estimand strategy). The strategy of handling intercurrent events for this endpoint is described in Table 1.

4.3.1.3. Change in SARS-CoV-2 Viral Load

Absolute and change from baseline in viral load in nasal secretions measured by qRT-PCR at Day 5, 8 and 11.

4.3.2. Main Analytical Approach

4.3.2.1. Binary Endpoints

The following secondary endpoints will be analysed as binary endpoints:

- Participants who have progression of COVID-19 (as defined in Section 4.3.1.1) through Day 29
- Participants who develop severe and/or critical respiratory COVID-19 (as defined in Section 4.3.1.2) through Day 29

The Safety analysis set will be used and the secondary binary endpoints will be summarized using counts and percentages, and listed (where appropriate). The estimands are described in Table 1. Missing data will not be imputed.

In addition, a shift table from baseline to the level of respiratory support (defined in the OPS) will be produced and the proportion of participants in each category will be summarised at each visit using a stacked bar chart. Individual participant profiles showing the time course of respiratory support will also be produced. A listing of oxygen supplementation will also be provided.

A summary of death will also be provided.

4.3.2.2. Continuous Endpoints

The following secondary endpoint will be analysed as a continuous endpoint:

- Change from baseline in viral load in nasal secretions measured by qRT-PCR at Day 5, 8 and 11

Note that the additional timepoints at which virology data is also collected i.e. Day 3 and 29 (as per Section 1.3 Schedule of Activities in the Protocol) will also be summarised in the above table. The Virology analysis set will be used and the change from baseline will be summarised on the $\log_{10}$ scale using descriptive statistics. The estimand is described in Table 1. When a sample is reported as 'NEG' (below lower-limit of detection) or '<2.08'

(below lower-limit of qualification), it is to impute as 0.5x120 copies/ml = 60 copies/ml =1.78 $\log_{10}$ copies/ml. Missing data will not be imputed.

Figures and listings will also be included where appropriate.

4.4. Other Safety Endpoints

Other safety endpoints are defined in Section 4.4.1 to Section 4.4.7. The analyses of those endpoints will be based on the Safety analysis set (unless otherwise specified) and the planned analyses is as described below.

4.4.1. Laboratory Data

Laboratory data will include clinical chemistry, hematology, coagulation and urinalysis. The summaries described below will only be produced for clinical chemistry, hematology and coagulation data.-Urinalysis data will only be listed.

Separate summaries of change from baseline for each laboratory test by visit, will be provided.

Summaries of maximum grade increase post-baseline from baseline will be provided for all the lab tests that are gradable by DAIDS 2017 Corrected 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.

For lab tests that have normal ranges, 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.

Note, the determination of the worst-case post-baseline in all the summaries above takes into account both planned and unscheduled assessments.

Laboratory data listings will also be provided.

Summaries of hepatobiliary laboratory events will be provided in addition to what has been described above. Possible Hy’s law cases will be presented in a plot for maximum post-baseline Total Bilirubin (xULN) against ALT (xULN). In addition, a plot of maximum ALT (xULN) versus baseline ALT (xULN) value for each participant will be produced.

In addition, for participants that have a liver Level 1 or Level 2 monitoring event, a listing of liver chemistry tests and a listing of liver monitoring event reporting will be produced (see Protocol Section 7.4). For participants that have a Level 2 monitoring event, a liver event profile will also be produced.

Additional laboratory figures may be provided where applicable (see OPS for further details).

4.4.2. Vital Signs

Vital sign data include blood pressure (systolic and diastolic), 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 for each test.

Vital sign data will also be provided in listings.

4.4.3. Electrocardiograms

The number and percentage of participants with ECG findings will be summarized by visit. The ECG findings to be summarized are the ECG interpretation, clinical significance of abnormal ECGs, and whether there was a clinically significant change from baseline (as ascertained by the PI). Participants with missing baseline values will be excluded from this summary.

A summary of change from baseline in ECG values will also be summarized by visit (refer to Section 6.2.3 for handling of triplicate ECG assessments for this summary).

ECG data will also be provided in listings.

4.4.4. Disease-Related Events (Not Classified as AEs) through Day 29

A summary of the number and percentage of participants with 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 form. This data will also be listed. Note, study day will be used to flag safety data through Day 29 for the safety endpoints through Day 29. For endpoints through Week 36, all safety data available in the database at the time of reporting the deliverable of interest will be used.

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 more than pre-morbid supplemental oxygen.
- hypoxemia due to COVID-19 requiring non-invasive ventilation, positive airway pressure devices, or high flow oxygen devices.

- respiratory failure due to COVID-19 requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

4.4.5. Multisystem Inflammatory Syndrome in Children (MIS-C) through Day 29 and Week 36

MIS-C cases will be defined as per the CDC definition [CDC, 2021e] and reported as AEs.

The number and percentage of participants with MIS-C through Day 29 and through Week 36 will be obtained from the summaries/listings of All AEs mentioned under Adverse Events in Section 4.2.2 above for the Day 29 SAC and the Week 36 SAC respectively. No additional outputs will be produced for this endpoint.

4.4.6. Extent of Exposure

Exposure data including duration of administration will be summarized in a table. Listings of data on participant exposure will also be generated.

4.4.7. Other Safety Measures

Physical examination and pregnancy tests (serum or high sensitivity urine results) will be captured in CRF. Participant listings will be provided.

A summary and listing of tolerability assessments will be provided (see OPS for details).

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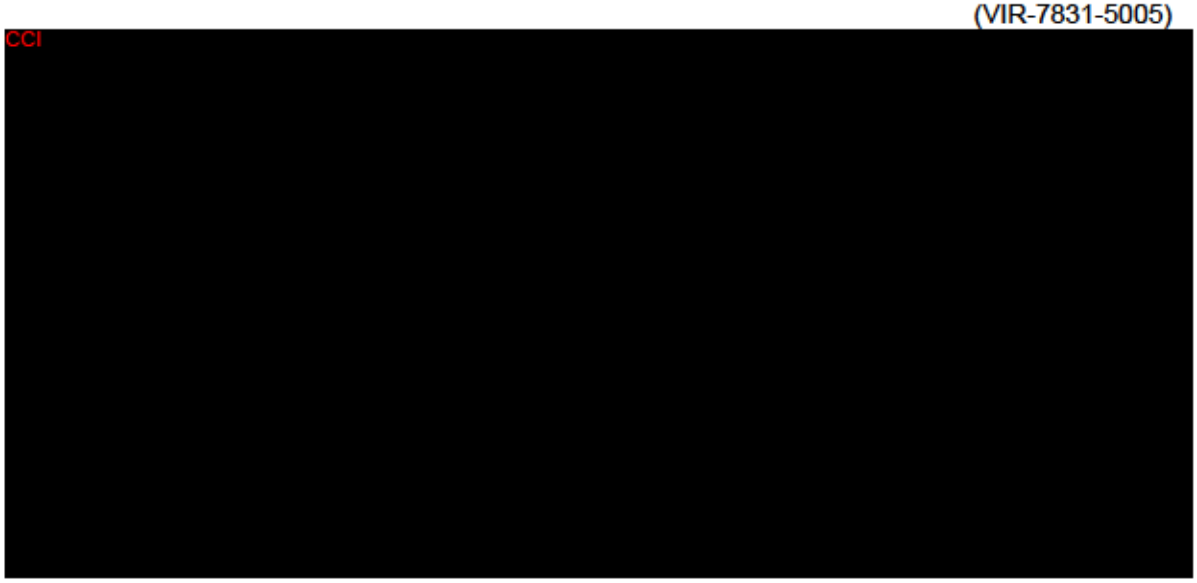

4.6. Other Analyses

4.6.1. Subgroup analyses

There is no pre-specified subgroup analysis planned.

4.7. Interim Analyses

In-stream reviews of the safety and PK data (when applicable) will be conducted at the following points:

Scheduled reviews – Cohort A:

- PK and safety data will be reviewed by the IDMC and the JSRT (only safety data) once all participants in Cohort A aged 12 to <18 years complete Day 29. This data will be reviewed along with IM efficacy data in adults, to decide whether to open recruitment to participants aged 2 to <18 years in Cohort B.
- Safety data will be reviewed by the IDMC and the JSRT once half of Cohort A participants ages 2 to <18 years complete Day 29. Data will be used to decide whether to open recruitment to participants aged from birth to <2 years in Cohort A. Note: For this review, updated PK data will also be provided to the IDMC, if available.
- Safety data will be reviewed by the JSRT after half of participants are dosed in Cohort A. Data will be used to decide whether the post-dose Day 1 monitoring should be reduced to 1 hour within Cohort A.

Scheduled reviews – Cohort B:

- Safety data will be reviewed by the IDMC and the JSRT once half of Cohort B participants ages 2 to <18 years complete Day 29. Data will be used to decide whether to open recruitment to participants aged from birth to <2 years in

Cohort B. Note: For this review, updated PK data will also be provided to the IDMC, if available.

- Safety data will be reviewed by the JSRT after half of participants are dosed in Cohort B. Data will be used to decide whether the post-dose Day 1 monitoring should be reduced to 1 hour within Cohort B.

For these scheduled reviews, the IDMC will review the study population, PK and safety data specified in the IDMC charter. The JSRT will review all emerging safety data and a separate project-level JSRT charter is available.

In addition, for Cohort A (12 to <18 years) Day 29, the JSRT and IDMC will review the primary PK and safety endpoints as described in Section 4.2.1 and Section 4.2.2.

Additional outputs may be provided to regulatory authorities (see OPS for further details).

Although this is an open-label, non-randomised study, randomisation schedule(s) will be created in Randall NG for programming purposes (i.e., to be able to use the standard HARP macros). For the Cohort A (12 to <18 years) Day 29 reporting, once the last participant recruited in this Cohort and age band completes Day 29, the data will be formally unblinded in the systems (e.g., Randall NG) for this age band only, to allow a readout of the primary endpoints for Day 29.

Further details of the required outputs for the scheduled reviews are provided in the OPS.

4.8. Full Day 29 and Week 36 Analyses

Once the last participant recruited in Cohort A completes Day 29 the data will be formally unblinded for all Cohort A participants to allow a readout of the primary endpoints for Day 29. This will be considered as the Cohort A Day 29 SAC. The same approach will be followed for Cohort B once the last participant recruited in Cohort B completes Day 29. This will be considered as the Cohort B Day 29 SAC.

Cohort A and Cohort B participants will continue to complete the remaining scheduled assessments up to Week 36. The final planned analyses will be performed after all participants have completed and data are available through Week 36. This will be considered the final Cohort A and Cohort B Week 36 SAC. See Section 4.2, Section 4.3, Section 4.4 and Section 4.5 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.

4.9. 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 9.4 Interim Analysis of the protocol Amendment 1 (Dated: 01-OCT-2021) specifies that interim analysis of safety and PK data will be conducted.	• An in-stream review of safety and PK data will be conducted at planned timepoints.	• Incorrect terminology has been used in Protocol Amendment 1 as there is no formal interim analysis that are planned to be conducted.
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• The protocol (Section 3 and Section 9.3.1) specified that the only intercurrent event considered in the study is the event of use of non-permitted medication. The strategy of handling this endpoint for all endpoints is defined as data analyzed as collected (treatment policy strategy) regardless of occurrence of the intercurrent events.	• Two additional intercurrent events have been added in this SAP: 1) An intercurrent event of participants receiving incomplete IV/IM dose has also been added. For the primary PK endpoints, a principal stratum strategy will be applied where we are only interested in the strata of participants who would be able to receive a complete IV/IM dose. A PK principal stratum analysis set has been defined (see Section 3. For all other endpoints where this intercurrent event could have an impact, a treatment policy strategy will be applied. 2) An intercurrent event of death. For the endpoint of development of severe and/or critical respiratory COVID-19 through Day 29, if a participant died prior to Day 29 without first having received supplemental oxygen, we would want to consider them as having met the endpoint (composite strategy).	• The additional intercurrent event of participants receiving incomplete IV/IM dose could have an impact on some of the endpoints including the primary endpoints. Thus, the estimand strategy for each endpoint and intercurrent event needs to clearly be defined. • For the endpoint of development of severe and/or critical respiratory COVID-19 through Day 29, the event of death needs to be accounted for.
• The protocol (Section 4.1) specified that only safety data will be	• The SAP (Section 4.7) specifies that updated PK data (if available) will also be provided and reviewed	• This has been updated in the SAP to reflect what is stated in the IDMC charter.

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
reviewed by the JSRT and IDMC once half of Cohort A/Cohort B participants ages 2 to <18 years complete Day 29. Data will be used to decide whether to open recruitment to participants aged from birth to <2 years in Cohort A/Cohort B.	by the IDMC for those in-stream reviews.	

5. SAMPLE SIZE DETERMINATION

Sample size determination for PK evaluation (IV and IM separately) was conducted using trial simulation methods. NHANES- and WHO-validated weight-for-age distributions for four standard age bands were simulated for large (n=72), medium (n=36), and small (n=24) trials with dense, medium and sparse sampling (5 samples per participant). A minimum of 1,000 trials were simulated per scenario using allometric scaling from preliminary adult PK data and fitted with a non-linear mixed effects PK model. Precision of estimation, together with degree of exposure matching to adult reference AUC_{inf} exposure was determined for all scenarios. The final trial design (36 participants and no more than 5 samples per participant) was simulated 10,000 times and final precision estimated for the four reference age bands. Precision of estimation **(**relative standard error [RSE]) for the primary endpoint (body weight-adjusted clearance) was less than 20%, which is well below the suggested 40% guidance for trials of this type.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Safety analysis set, unless otherwise specified. Results will be presented by Cohort. Please see Section 3 of the SAP for more information on analysis sets.

6.1.1. Participant Disposition

A summary of participant status and participant disposition for the study conclusion record will be provided. This display will show the number and percentage of participants 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 participant is considered to have completed the study if he/she has completed the Week 36 visit. Participants who withdrew from the study together with their reasons for withdrawal will also be listed.

A summary of participants that discontinued study treatment together with their reasons for discontinuation will be provided. In addition, a listing of participants that

discontinued or interrupted study treatment together with their reasons for discontinuation/interruption will be presented.

A summary of the number and percentage of participants 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 for those participants who failed screening. This summary will be produced based on the Screened analysis set. Participants with screen failure and reason for screen failure will be listed.

The number of participants will be summarized by Country, Site Id. and Investigator Id. on the Enrolled analysis set and the Safety analysis set. This will be repeated on the PK principal stratum analysis set if required (see OPS for further details).

A summary of the duration in days since infusion/injection will be summarized categorically (see OPS for further details). The summary may also be displayed by mortality status: alive or deceased, if there are ≥2 deaths.

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

A listing of planned and actual treatments will be provided.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, baseline BMI) will be summarized by descriptive statistics and listed. Age ranges will be summarized in a separate table. The race and race combination details of participant will also be summarized in a table and listed. The summary of demographic characteristics may be repeated on the PK principal stratum analysis set and Virology analysis set if required (see OPS for further details).

In addition, the past and current medical conditions will be summarized in two separate tables. A listing will also be provided.

Family history of cardiovascular risk factors will be summarized and listed.

Liver medical history will also be summarized and listed.

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), types of symptoms present and symptom duration will be summarized.

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 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 any inclusion and exclusion criteria and corresponding criteria that were violated will be listed.

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 number and percentage of participants taking concomitant medications will be summarised by Anatomical Therapeutic Chemical (ATC) Level 1 (Body System) and by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Concomitant Medications will be summarized, while prior and concomitant medications will be listed.

6.1.5. Substance Use

Substance use of tobacco will be collected in CRF (only for those ≥2 years of age). 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 2 Data Derivations Rule

6.2.1. Study Period

Study phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is prior to study treatment start
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.

6.2.2. Study Day and Reference Dates

The safety and PK reference date is the study treatment 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 Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.3. Multiple measurements at One Analysis Time Point

During screening and during post-baseline visits, triplicate ECG assessments may be taken. The 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 (even if the local lab ones are worse). If multiple assessments are taken from the same type of lab, the latest record will be used (see OPS for further details).

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

Participants having both High and Low values for DAIDS 2017 Corrected v2.1 or Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Worst case post-baseline" row of related summary tables.

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

6.2.4. 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 participant 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

Element	Reporting Detail
Safety and PK Endpoints	• No missing data imputation will be performed for safety or PK endpoints. • Data will be reported as captured.

6.2.5. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• 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).
Adverse Events	• Partial dates for AE recorded in the CRF will be imputed using the following conventions:

Missing start day	• If study treatment start date is missing (i.e. participant 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.

Missing start day and month	• If study treatment start date is missing (i.e. participant 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.

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	No Imputation
Completely missing start/end date	No imputation

<table>
<tr><th>Element</th><th>Reporting Detail</th></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. participant 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. participant 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>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>
<tr><td>Oxygen Supplementation</td><td>
<table>
<tr><td>Completely missing end date</td><td>If the end date is missing and a subsequent record exists and it 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 the time of the database extraction.</td></tr>
</table>
</td></tr>
</table>

6.2.6. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
CCI [redacted]

6.3. Appendix 3 Handling of Serum Concentrations Below the Assay's Lower Limit of Quantification (BLOQ)

Serum concentrations below the assay's lower limit of quantification (BLOQ) will be handled as per Section 3.5.1 of the GSK R&D Guideline: [redacted] For ease of review, Section 3.5.1 of the guidance is also provided in this appendix.

For the calculation of individual pharmacokinetic profiles

If one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration. For linear plots, zero concentration value(s) before the first measurable concentration will be included in the plot. For log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value.

If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots.

If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual subject plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).

NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of pharmacokinetic parameters and from the individual subject plots.

In some circumstances, there may be a pharmacokinetic rationale for fluctuation resulting in non-measurable concentrations in the middle of the concentration-time profile (e.g., entero-hepatic recycling, erratic absorption from transdermal/inhaled formulations). In these cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) and subsequent valid concentrations may be retained. A reference line indicating LLQ will be included in plots.

For the calculation of mean or median pharmacokinetic profiles

When estimating the mean or median value for the concentration at a given time point (i.e., descriptive mean or median curve), the following guidelines should be considered:

All NQ values will be set to zero except when an individual NQ falls between two quantifiable values, in which case it will be omitted from the calculation of mean or median profiles. Measurable concentrations which follow more than one consecutive mid-profile NQ will be omitted (set to missing).

The mean/median value at a time-point where one or more samples have NQ values will be reported (in tabular or graphical fashion) even if the mean/median value is below the LLQ of the assay. For linear plots, zero concentration value(s) will be included in the plot. For log-linear plots, zero concentration value(s) will be assigned a missing value. Zero mean or median values will be included in summary tables.

In certain cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) with proper scientific justification(s). A reference line indicating LLQ will be included in plots.
It should be noted that a high proportion of NQ values may affect the standard deviation (SD); if more than 30% of values are imputed, then SD will not be displayed. Any table of summary statistics for concentration-time data will report N (number of subjects in the analysis population), n (number of subjects with non-missing values) and number imputed (number of subjects with imputed values (i.e., NQ assigned zero concentration).

BQL (Below the Quantification Limit) may be displayed in listings by legacy systems instead of NQ; these abbreviations are interchangeable and mean that a sample has been received, analysed and a concentration below the LLQ of the assay found. Scientific judgement and prior knowledge should always be used in applying these guidelines.

7. REFERENCES

Centers for Disease Control and Prevention (CDC). Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). https://www.cdc.gov/mis/hcp/index.html. Page last reviewed May 20, 2021. Accessed September 15, 2021(e).

Vir Document: VIR-7831-5005 Protocol Amendment 1 (GSK Study ID 215226). An open-label, non-comparator, multicenter study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous or intramuscular dose of sotrovimab in pediatric participants with mild to moderate COVID-19 at high risk of disease progression. Effective Date: 01 October 2021