**Protocol**

**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

**Date of Document:** 01-Oct-2021

# 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

**Protocol Number**: GSK Study 215226/VIR-7831-5005 Amendment 1

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

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

**Study Phase:** Phase 2b

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

**Sponsor Name and Legal Registered Address:**

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**Regulatory Agency Identifying Number(s):**

| Registry | ID |
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| IND | 154430 |
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**Approval Date:** 01-OCT-2021

## SPONSOR SIGNATORY:

**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

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| | |
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Andrew Skingsley
Clinical Development Lead, M.D.

**Date**

***The signed page is a separate document.***

**Medical Monitor Name and Contact Information** can be found in the Study Reference Manual

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| **DOCUMENT HISTORY** | | |
|---|---|---|
| **Document** | **Date** | **Document Identifier** |
| Amendment 1 | 01-OCT-2021 | TMF-13971114 |
| Original Protocol | 11-AUG-2021 | TMF-13858781 |

**Amendment 1** 01-OCT-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for the Amendment:**

The rationale for this amendment is to 1) update the dosing scheme to use weight-based dosing per United States Food and Drug Administration (FDA) feedback, 2) to make intramuscular (IM) dosing contingent on confirmation of the efficacy of IM dosing in adults, 3) to include occurrence of multisystem inflammatory syndrome in children (MIS-C) as an objective per European Medicines Agency Pediatric Committee request and 4) to align blood sample collection volumes in participants <2 years to be within acceptable limits set out by the National Institute of Health (NIH) directives.

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 1.1. Synopsis; 1.2 Schema; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 4.3. Justification for Dose; 6.1. Study Intervention(s) Administered | Updated dosing scheme and justification to include weight-based dosing for all participants (Section 1.1, Section 4.3, and Section 6.1) and to make the initiation of intramuscular (IM) dosing dependent on efficacy of IM dosing in adults (Section 1.1, Section 1.2, Section 4.1, and Section 4.2). | Changes made to address FDA feedback regarding dosing. |
| 1.3. Schedule of Activities (SoA); 3. Objectives, Endpoints, and Estimands; 5.2 Exclusion Criteria; 8.5.7. Monitoring of Multisystem Inflammatory Syndrome in children (MIS-C) | Added the following endpoint to the Other Safety endpoints: occurrence of multisystem inflammatory syndrome in children (MIS-C) through Day 29 and Week 36. Specified in the SoA that events of MIS-C are collected as adverse events. Clarified MIS-C diagnoses | Added endpoint at the request of the European Medicines Agency Pediatric Committee and clarified the MIS-C reporting and diagnosis criteria to be used for this endpoint. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | criteria in the exclusion criteria and in Section 8.5.7. | |
| 1.1. Synopsis; 1.3. Schedule of Activities (SoA); 4.1. Overall Design; 8.3.1. SARS-CoV-2 Serology Analysis | Created a new SoA for participants <2 years of age. For participants <2 years of age, removed blood samples for anti-nucleocapsid and anti-spike SARS-CoV-2 antibodies and removed Day 8 pharmacokinetic sample. | Updated procedures for participants <2 years of age to keep blood sample volume within acceptable limits set forth by NIH directives. |
| 3. Objectives, Endpoints, and Estimands | Updated the objective and endpoint for assessment of the effects of sotrovimab on SARS-CoV-2 antibodies to state that this will only be assessed in participants ≥2 years of age. | To keep blood sample volumes within acceptable limits set forth by NIH directives, participants <2 years of age will not have blood drawn for the purpose of SARS-CoV-2 antibody assessment. |
| 1.3. Schedule of Activities (SoA) | Separated coagulation studies from hematology and chemistry studies in the SoA and updated the study days for which coagulation studies will be performed. | Coagulation studies are only clinically required at Screening and Day 1. |
| 1.1. Synopsis; 4.1. Overall Design; 4.3. Justification for Dose; 6.1. Study Intervention(s) Administered | Updated cut-off for saline dilution. Cut-off is now weight-based instead of age-based. | Updated to keep endotoxin levels within acceptable limits for the new dosing scheme. |
| 1.1. Synopsis; 2.3.1. Risk Assessment; 4.1. Overall Design; 8.5.1. Vital Signs; 8.6.9. Adverse Events of Special Interest; 9.4. Interim Analysis; 10.1.5.1. Joint Safety Review Team | Modified the timing of JSRT review from two-thirds of participants dosed in any age band in either cohort to half of participants in either cohort | Modified the timing of JSRT since larger number of participants can be dosed in a shorter period of time, which will be helpful to assess sotrovimab's safety and tolerability profile across the age bands sooner. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8. Study Assessments and Procedures | Updated blood sampling volumes to be within acceptable limits. | Revised blood sampling volumes to be consistent with European Medicines Agency guidelines for participants ≥2 years of age and with NIH guidelines for participants <2 years of age. |
| 1.1. Synopsis; 1.2. Schema; 1.3. Schedule of Activities (SoA); 2.3.1. Risk Assessment; 3. Objectives, Endpoints, and Estimands; 4.1. Overall Design; 4.4. End of Study Definition; 5.1. Inclusion Criteria; 8.4.3. Phone Call for Subsequent COVID-19 Illness; 8.5.6. Pregnancy Testing; 8.6.1. Time Period and Frequency for Collecting AE and SAE Information; 8.6.6. Pregnancy; 8.6.9. Adverse Events of Special Interest; 9.3.1. Primary Endpoint(s); 9.4. Interim Analysis | Changed follow-up period to 36 weeks after dosing. In Section 8.4.3, the weekly phone call is extended to Week 35 based on the new follow-up period. | Follow-up period changed to be consistent with FDA requests for follow-up duration in light of new product half-life, which is also consistent with other clinical protocols for sotrovimab. |
| 5.2. Exclusion Criteria | Updated exclusion criteria number 14 to clarify restrictions on receipt of authorized or approved SARS-CoV-2 vaccines. | Updated criteria based on CDC guidelines. |
| 1.3. Schedule of Activities (SoA); 5.1. Inclusion Criteria; 8.5.6. Pregnancy Testing | Updated wording for inclusion criteria number 5 to specify that contraception and pregnancy testing are only required for female participants as appropriate for the age and sexual activity of pediatric participants and as required by local regulations and added that | Clarified that pregnancy testing and contraception are only required for women of child-bearing potential. Participants who are breastfeeding a child are not included in this study based on possible |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | female participants cannot be breastfeeding. Updated other sections to be consistent with the inclusion criteria. | risks of sotrovimab exposure. |
| 5.2. Exclusion Criteria | Updated the respiratory rate by age for exclusion criteria 3. | Used age-based criteria established by *The Pediatric Emergency Medicine Resource* (American Academy of Pediatrics and the American College of Emergency Physicians) instead of category-based criteria from the *Pediatric Advanced Life Support* (American Heart Association). |
| 1.3. Schedule of Activities (SoA); 8.3. Virologic Assessments | Clarified that the nasal mid-turbinate swab for virology and resistance analyses on Day 1 will be collected pre-dose | Added information to clarify the sampling times. |
| 10.2 Appendix 2: Clinical Laboratory Tests | Specified that Screening laboratory assessments for all participants and all safety laboratory assessments for participants <2 years of age will be performed by a local laboratory. | Screening laboratory assessment will be performed locally in order to have results of hematology and coagulation prior to intramuscular dosing. Furthermore, all laboratory assessments will be performed locally for participants <2 years of age in order to keep the total blood volume within acceptable limits based on guidelines for pediatric participants. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.2 Appendix 2: Clinical Laboratory Tests | Added details regarding urinalysis safety laboratory assessments. | Added additional explanation on the nature of the analysis and conditions to perform microscopic urine analysis. |
| 1.1. Synopsis; 4.1. Overall Design; 6.1. Study Intervention(s) Administered | Removed the age restriction for anterolateral thigh injections. Changed description from ventrolateral to anterolateral thigh. | Anterolateral thigh is an acceptable location for IM injections for all ages.<br><br>Anterolateral thigh is the preferred term for this injection location. |
| 9.4. Interim Analysis | Added interim analysis of safety and PK data. | Review of the data that will be used for determining if the study can proceed to the next recruitment step and whether monitoring time can be reduced will be considered as interim analysis. |
| 1.3. Schedule of Activities (SoA) | Specified which visits must be done at the study site. | Clarified that Screening and Day 1 study visits must be done at the site. |
| 8.5.5. Clinical Safety Laboratory Tests | Removed bullet point that stated the use of heel sticks should be avoided. | Heel sticks or other capillary draw methods may be necessary in order to keep blood sample volumes within acceptable limits for participants <2 years of age. |
| 1.3 Schedule of Activities (SoA); 2.3.1. Risk Assessments; 4.2. Scientific Rationale for Study Design; 7.2. Participant Discontinuation/Withdrawal from the Study; 8. Study Assessments and Procedures; | Revised wording for the local injection site tolerability and pharmacokinetic footnotes in the SoA; corrected wording in Section 2.3.1 regarding the procedure for JSRT review of safety data for reduced monitoring time; clarified in | Updates made for clarity and consistency. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.1.4. Data Protection; 10.8. Appendix 8: World Health Organization (WHO) Weight-For-Age Curves | Section 2.3.1 the enrollment of participants who have conditions that contraindicate IM injections; corrected description of secondary endpoints in Section 4.2; clarified participant withdrawal procedures in Section 7.2; clarified storage of blood samples in Section 8; clarified the disclosure of pregnancy and contraception information to legal guardian in Section 10.1.4; provided chart titles for the WHO references in Section 10.8. | |
| 1.1. Synopsis; 2.1. Study Rationale; 2.2.1 Clinical Experience with Sotrovimab; 2.3.1 Risk Assessment; 2.3.2. Benefit Assessment | Provided updated information. | Updated sections to provide more recent information about sotrovimab. |
| Title Page | Added EudraCT number. | The EudraCT number was issued for this study. |
| Title Page; Sponsor Signature Page | Changed order of the list of compound names to put sotrovimab first. Moved Vir study number to the line for protocol number. | Updated for consistency with other sotrovimab protocols. |
| 10.10 Abbreviations and Trademarks | Updated abbreviations list. | Updated abbreviations to reflect in-text changes. |
| 11. References | Added and removed references. | Updated references to reflect in-text changes. |
| All sections | Other minor grammatical and typographical corrections. | To improve readability. |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**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

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

**Rationale:**
There is an urgent medical need for therapeutics for the treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19). Early treatment of mild and moderate disease in outpatients could prevent the more severe sequelae of COVID-19 requiring hospitalization, such as respiratory failure, and non-respiratory complications of COVID-19 including thromboembolic disease leading to pulmonary embolism and stroke, myocardial injury and arrhythmias, renal failure, and shock, among others. Furthermore, a potent treatment given early in disease could ameliorate the severity and duration of COVID-19 and potentially reduce transmission.

Throughout the COVID-19 pandemic, a number of risk factors have come to be associated with worse clinical disease in adults: advanced age and patients with comorbidities such as obesity, diabetes, hypertension, chronic kidney disease, and congestive heart failure were more likely to have severe disease requiring hospitalization or die. While children are more likely than adults to have asymptomatic or mild infection, they account for more than 14% of total cases since the pandemic began and comprise 19% of all new COVID-19 cases for the week ending on 10 June 2021 and significant morbidity and mortality can also be seen during acute infection. Between 04 January 2021 and 20 June 2021, approximately 15.8% of 4.79 million COVID-19 cases reported in the European Economic Area (EEA), excluding the United Kingdom (UK), were in children (those aged 18 years and under). Children have comprised an increasing proportion of weekly COVID-19 case numbers since January 2021, with the largest increase among those aged 5 to 11 years. This increasing proportion of weekly cases in children corresponds with the start of vaccination rollout in the European Union (EU)/EEA**.** Pediatric patients with COVID-19 are more likely to be hospitalized with severe disease or die if they are young (≤1 year) or have a history of obesity, gastrointestinal conditions, congenital heart disease, genetic or metabolic conditions, neurologic disease, diabetes mellitus, asthma or chronic lung disease, immunosuppression, sickle cell disease, or baseline medical complexity. Furthermore, multisystem inflammatory syndrome in children (MIS-C) represents a rare complication of SARS-CoV-2 infection observed in children and recently a similar syndrome in adults, multisystem inflammatory syndrome in adults (MIS-A), has also been observed. Multisystem inflammatory syndrome in children generally presents between 2 to 6 weeks following SARS-CoV-2 infection, suggesting a post-infectious complication potentially driven by formation of pathogenic autoantibodies.

Although severe COVID-19 in any age group puts strain on healthcare systems, severe COVID-19 in a pediatric population can be particularly problematic in the absence of local or regional hospitals equipped to treat severely ill children.

For early treatment of non-hospitalized pediatric patients with mild-to-moderate COVID-19 at high risk of progression to severe disease, the monoclonal antibody (mAb) combinations of bamlanivimab/etesevimab and casirivimab/imdevimab have been authorized (Emergency Use Authorization [EUA]) in adolescents aged 12 to 18 years (≥40 kilograms [kg]) for prevention of disease progression. However, on 25 June 2021, the Department of Health and Human Services (HHS) halted the distribution of bamlanivimab/etesevimab in the United States of America (US) due to their lack of activity against the Gamma variant (Brazil) and the Beta variant (South Africa).

Other treatments including remdesivir, baricitinib, remdesivir/baricitinib and dexamethasone (off-label use) in children are exclusively recommended for severe or critical COVID-19.

There are no other treatment options approved for children, none for children below the age of 12 years with mild-to-moderate COVID-19, and none for children under the age of 2 years with severe disease. Further, the route of administration for existing mAb combinations is intravenous (IV) with 20 to 70 minute infusion times for outpatients at a time when patients are still infectious and access to facilities for IV administration has been a rate-limiting step. Given the time required for infusion of other authorized mAbs and the limited outpatient availability of sites for infusion, strategies that allow for treatment at pharmacies, primary care clinics, and other point-of-diagnosis sites will unburden the healthcare system and offer the opportunity to reach more pediatric patients—especially in sites that do not have pediatric specialty care.

Therefore, there is an urgent need for the development of new treatment modalities with an accessible administration route (intramuscular [IM]) and preserved activity against emerging SARS-CoV-2 variants.

Vir Biotechnology, Inc. (Vir) has developed a human neutralizing anti-SARS-CoV-2 antibody, VIR-7831 (GSK4182136, hereafter referred to as sotrovimab), which has an Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life ($t_{1/2}$). In humans, sotrovimab has a $t_{1/2}$=48.8 days. Sotrovimab binds with high affinity to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. Vir Biotechnology, Inc and GlaxoSmithKline (GSK) are collaborating on the development of sotrovimab for the treatment of COVID-19, including the use of sotrovimab via IV infusion and IM injection.

Sotrovimab (500 mg, IV) was assessed in participants with COVID-19 in an early treatment study, VIR-7831-5001 (GSK Study 214367, also known as COMET-ICE [NCT04545060]), with the aim of preventing disease progression in non-hospitalized participants. For the first planned interim analysis, the Independent Data Monitoring Committee (IDMC) met on 10 March 2021 and reviewed data from 583 participants. The IDMC recommended halting enrollment in the trial due to overwhelming efficacy, with an 85% reduction in the risk of hospitalization or death in the sotrovimab arm versus the placebo arm (primary endpoint). The results of this study supported the Emergency

Authorization submissions. Emergency authorizations and/or marketing approvals for sotrovimab (Generation2 [Gen2]) for the treatment of mild-to-moderate COVID-19 have been received in the US on 26 May 2021 (EUA), positive opinion via Article 5(3) in the EU on 20 May 2021, Canada on 30 July 2021 (Interim Order), Singapore on 30 June 2021 (Pandemic Special Access), Italy on 29 July 2021 (Temporary Authorization) and Australia on 20 August 2021 (Provisional Marketing Authorization). Similar emergency use applications have also been approved in the United Arab Emirates, Bahrain, Kuwait, Qatar, Oman, Switzerland, Egypt, Brazil, and a conditional marketing approval in Saudi Arabia.

Sotrovimab has been formulated to allow for either IV or IM administration. Administration via IM dosing could allow greater access to mAb treatment without the requirement of facilities for IV administration. The IM administration is currently being evaluated in a study to evaluate safety, tolerability, pharmacokinetics (PK), and viral pharmacodynamics (PD) of sotrovimab administered intravenously or via IM injection in participants with mild to moderate COVID-19 (VIR-7831-5006/GSK Study 216912, also known as COMET-PEAK; NCT04779879) and in a Phase 3 study (COMET-TAIL [VIR 7831-5008/GSK Study 217114; NCT04913675]) to assess the efficacy, safety, and tolerability of sotrovimab given IM versus IV for the treatment of mild/moderate COVID-19 in high-risk non-hospitalized participants. The COMET-TAIL study is evaluating the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab for the prevention of progression of COVID-19 in a non-inferiority setting and includes enrollment of adolescent participants between the age of 12 to 17 years.

Sotrovimab is a dual action mAb derived from the parent antibody S309 identified from a 2003 SARS-CoV survivor. It targets a highly conserved epitope in the region of the spike RBD that does not compete with angiotensin converting enzyme 2 (ACE2) binding and is outside of the receptor-binding motif (RBM). Furthermore, this epitope does not overlap with mutations in current variants of concern and continues to be highly conserved; additionally, sotrovimab has a high barrier to resistance observed *in vitro*.

Pseudotyped virus-like particle *in vitro* assessments indicate that sotrovimab retains activity against the UK (Alpha, B.1.1.7; 2.30-fold change in $EC_{50}$ value); South Africa (Beta, B.1.351; 0.60-fold change in $EC_{50}$ value); Brazil (Gamma, P.1; 0.35-fold change in $EC_{50}$ value); California (Epsilon, B.1.427/B.1.429; 0.70-fold change in $EC_{50}$ value); New York (Iota, B.1.526; 0.6-fold change in $EC_{50}$ value), India (Kappa, B.1.617.1; 0.7-fold change in $EC_{50}$ value, Delta, B.1.617.2; 1-fold changed in $EC_{50}$ value, Delta Plus [AY.1; 1.1-fold change in $EC_{50}$ value and AY.2; 1.3-fold change in $EC_{50}$ value]) and Peru (Lambda, C.37; 1.5-fold change in $EC_{50}$ value) variant spike proteins. Microneutralization data from authentic SARS-CoV-2 variant virus also indicate that sotrovimab retains activity against the UK (3-fold change in $EC_{50}$ value), South Africa (1.2-fold change in $EC_{50}$ value) and Brazil (1.6-fold change in $EC_{50}$ value) variants.

This study will evaluate the PK, safety, and PD of sotrovimab administered IM or IV in children from birth to less than 18 years old with mild-to-moderate COVID-19 at high risk of disease progression.

## Objectives, Endpoints, and Estimands:

| Objectives | Endpoints[a] | Other Estimand Attributes |
|---|---|---|
| **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<br>• 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) | Population: PK (all participants in Cohort A/Cohort B who are exposed to study intervention and who had at least 1 non-missing PK assessment [non-quantifiable values will be considered as non-missing values])<br>Summary measure: PK model parameters |
| To evaluate the safety and tolerability of sotrovimab by IV or IM administration | • Incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESI) through Day 29 and Week 36 | Population: Safety (all participants who are exposed to study intervention in Cohort A/Cohort B)<br>Summary measure: Counts and percentages |
| **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<br>*An attended medical visit includes visit to a hospital emergency room for management of illness or hospitalization for acute management of illness | Population: Safety<br>Summary measure: Counts and percentages |

| Objectives | Endpoints[a] | Other Estimand Attributes |
|---|---|---|
| | • Development of severe and/or critical respiratory COVID-19 as manifested by requirement for supplemental oxygen through Day 29*<br><br>*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 | Population: Safety<br><br>Summary measure: Counts and percentages |
| 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 | Population: Virology (all participants who are exposed to study intervention in Cohort A/Cohort B and have a quantifiable SARS-CoV-2 viral load measurement at baseline)<br><br>Summary measure: Arithmetic mean |

Abbreviations: ADA = anti-drug antibodies; AEs = adverse events; AESI = adverse events of special interest; anti-N = anti-nucleocapsid; $AUC_{inf}$ = 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 intervention.

**Overall Design:**

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 B initiation will be contingent upon 1) acceptable PK and safety from adolescents aged 12 to <18 years in cohort A and 2) data from COMET-TAIL supporting the efficacy of IM dosing in adults. The exposure-response relationship has not yet been established for sotrovimab in adults following IM administration. This will be determined after the read-out from the COMET-TAIL study and will be used to support initiation of IM administration and enrollment in Cohort B.

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.

Participants will be enrolled into the following age bands for both Cohort A and Cohort B:

- Adolescents aged 12 to less than 18 years
- Children aged 6 to less than 12 years
- Children aged 2 to less than 6 years
- Birth to less than 2 years.

**Brief Summary:**

The purpose of this study is to assess the pharmacokinetics (PK), safety, and pharmacodynamics (PD) of sotrovimab administered via intravenous (IV) infusion or intramuscular (IM) injection in pediatric participants (aged from birth to <18 years) with mild/moderate COVID-19 at high risk of disease progression. Participants will be enrolled in one of two cohorts (Cohort A or Cohort B). Participants in Cohort A will receive IV sotrovimab and participants in Cohort B will receive sotrovimab via IM injections.

- Study Duration: 36 weeks
- Treatment Duration: A single dose of sotrovimab will be administered by IV infusion or administered intramuscularly on Day 1.
- Visit frequency: Participants will be screened at the study site. Participants will be dosed at the study site on the same day as Screening or within 2 days after Screening. The day of dosing is referred to as Day 1. Participants will have a home visit or will return to the study site on Days 3, 5, 8, 11, 14, 22, and 29, as well as on Week 12 and Week 36, after dosing for follow-up visits. COVID-19 disease progression will be monitored daily from Day 1 through Day 14 and on Day 22 and Day 29 (monitoring will be via a phone call on days when a home visit or clinic visit is not scheduled). Additionally, a weekly phone call will be

conducted starting at Week 5 on weeks when there is not a scheduled clinic/home visit. Participants in both Cohorts will have nasal mid-turbinate swabs for virology and resistance analyses and will have blood drawn for assessment of PK, anti-drug antibodies (ADA), and for safety assessments during the study. Participants ≥2 years of age will also have blood drawn for assessment of anti-nucleocapsid and anti-spike SARS-CoV-2 antibodies.

**Number of Participants:**

Cohort A and Cohort B will each enroll[1] approximately 36 participants; therefore, a total of approximately 72 participants will be enrolled in 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:

- 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.

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

[1] For this study, "enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after Screening.

ensure that the target number of participants in each Cohort and in each age band will receive IV infusion or IM injection.

**Intervention Groups and Duration:**

Dosing will be performed within 2 days of the Screening assessment. Dosing must occur ≤7 days from onset of COVID-19 symptoms. Screening can occur on the same day as dosing. Eligible participants will be treated with a single IM or IV dose of sotrovimab on Day 1 and followed for up to 36 weeks.

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<br>5 to <15 kg<br>15 to <40 kg | 62.5<br>125<br>250 | 1<br>2<br>4 |
| 2 to <6 years | 5 to <15 kg<br>15 to <40 kg | 125<br>250 | 2<br>4 |
| 6 to <12 years | 15 to <40 kg<br>≥40 kg | 250<br>500 | 4<br>8 |
| 12 to <18 years | 15 to <40 kg<br>≥40 kg | 250<br>500 | 4<br>8 |

Intravenous sotrovimab will be administered undiluted using a syringe pump for participants <15 kg, and diluted in 40 mL saline for participants ≥15 kg. Because endotoxin specification limits for sotrovimab exceeds allowable levels for infants weighing <1.88 kg, infants <2 kg will be excluded from the study. Intramuscular sotrovimab may be administered in dorsogluteal, anterolateral thigh, or deltoid muscles. Location of IM injections will be per participant/legally authorized representative [LAR] preference and the clinical discretion of the investigator.

After IV infusion or IM injection of sotrovimab, 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.

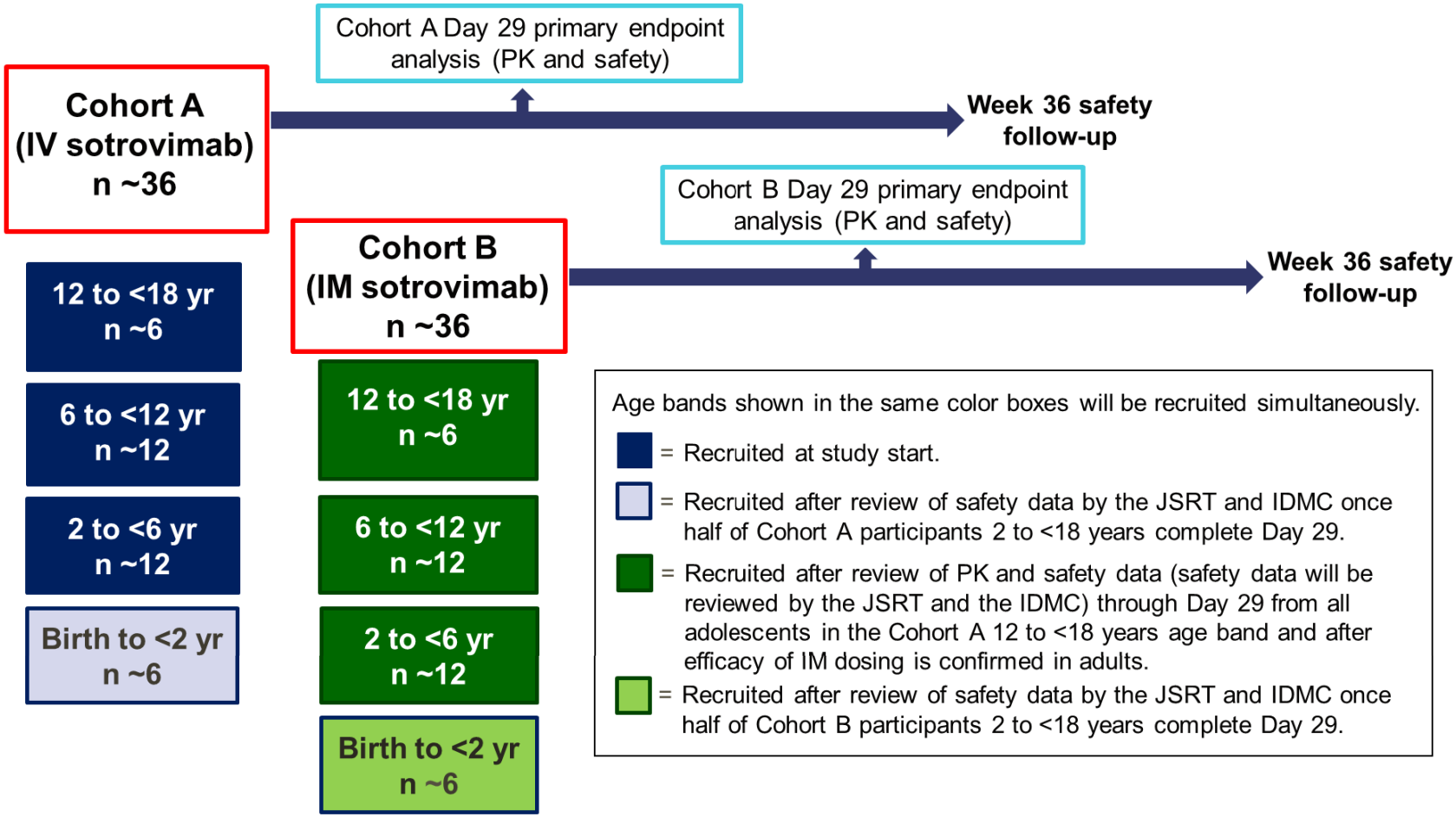
All participants in Cohort A and Cohort B will be actively monitored on an outpatient basis for 36 weeks after dosing (i.e., Week 36). Monitoring will occur by home or clinic visits and phone calls throughout the 36 week period.

**Data Monitoring/ Other Committee:**

An IDMC will review safety data throughout the conduct of the study at regular intervals as outlined by the IDMC charter. The roles and responsibilities of the IDMC, including membership, scope, frequency of meetings, and communication plan are defined in the IDMC charter.

A JSRT comprised of team members from clinical research, global safety, and statistics from GSK and Vir, will review safety data throughout the study and will determine if a safety concern identified during instream data review needs to be escalated to the IDMC. The responsibilities of the JSRT and frequency of assessments will be outlined in the JSRT charter.

## 1.2. Schema




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

## 1.3. Schedule of Activities (SoA)

### Table 1 SoA for Participants ≥2 Years of Age

| | Study Visit Day ± Visit Window | Screening[1] (Day -2, -1, or 1) | Day 1[1] | Day 3 | Day 5 | Day 8 | Day 11 | Day 14 | Day 22 | Day 29 ± 3d | Week 12 (Day 85 ± 7d) | Week 36 (Day 252 ± 14d) End of study (EOS) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Clinic (C) or home (H) visit | C | C | C/H | C/H | C/H | C/H | C/H | C/H | C/H | C/H | C/H |
| | Informed consent | X | | | | | | | | | | |
| | Demography | X | | | | | | | | | | |
| | Medical history (including baseline COVID-19 symptoms, comorbidities, and tobacco use) | X | | | | | | | | | | |
| | Eligibility criteria | X | | | | | | | | | | |
| | Study intervention administration | | X[2] | | | | | | | | | |
| Assessments | Physical examination (F=full, B=brief) | F[3] | F[3] | | | B | | B | B | B | | |
| Assessments | COVID-19 signs/symptoms review | X | X | | | X | | X | | X | X | X |
| Assessments | Monitoring of COVID-19 disease progression | | <----------X (Daily)[4]----------> | | | | | | X | X | | |
| Assessments | Phone call for subsequent COVID-19 monitoring | | | | | | | | | | Weekly from Week 5 to Week 11[5] | Weekly from Week 13 to Week 35[5] |
| Assessments | Vital signs (including blood pressure, pulse rate, respiratory rate, temperature, and oxygen saturation) | X | X[6] | X | X | X | | X | X | X | X | X |
| Assessments | 12-lead ECG[7] | X[7] | X[7] | | | X | | | | | | |
| Assessments | Local injection site tolerability assessment (IM only)[8] | | X[8] | X | X | X | | | | | | |
| Sample collection | Urine studies | X[9] | X[9] | | | X | | | | X | | |
| Sample collection | Hematology and chemistry studies | X[9] | X[9] | | | X | | X | | X | | |
| Sample collection | Coagulation studies | X[9] | X[9] | | | | | | | | | |
| Sample collection | Pregnancy test[10] | X | | | | | | | | | | X |
| Sample collection | SARS-CoV-2 diagnostic test (if not previously confirmed, point-of-care or local laboratory test) | X[11] | | | | | | | | | | |
| Sample collection | Nasal mid-turbinate swab for virology and resistance analyses | | X[12, 14] | X | X | X | X | | | X | | |
| Sample collection | Blood sample for PK analysis | | X[13] | | X | X | | | | X | X | |
| Sample collection | Blood sample for anti-drug antibody | | X[14] | | | | | | | X | | X |
| Sample collection | CCI | | CCI | | | | | | | CCI | | |
| Sample collection | | | X[14] | | | | | | | | | |
| | AE review[15] | | <----------X----------> | | | | | | | | | |
| | SAE review[16] | X[16] | <----------X----------> | | | | | | | | | |
| | Concomitant medication review | <----------X----------> | | | | | | | | | | |

**Notes:** in case of early discontinuation (ED) or withdrawal (EW), all Week 36 activities should be performed.

1. All Screening procedures must be completed within 2 days prior to dosing. When possible, Screening and dosing (Day 1) can be done on the same day. Contact information for secondary contacts will be collected at Screening and information about health care providers/facilities may also be collected at Screening.
2. Dosing will be performed ≤7 days from the onset of symptoms. Participants will be monitored for 2 hours after dosing. If the Joint Safety Review Team (JSRT) recommends reducing to 1 hour monitoring (see Section 10.1.5.1): Participants will be monitored for approximately 1 hour post-dose.
3. Including height, weight, and body mass index (BMI). The full physical examination only needs to be performed once if Screening and dosing occur on the same day.
4. Daily assessment will be via a phone call when a clinic or home visit is not scheduled.
5. Weekly phone call from Week 5 to Week 11 and Week 13 to Week 35 to assess for the incidence and severity of subsequent COVID-19 illness, if any. Weekly assessments must be performed within ±1 day of the scheduled phone call.
6. Record Day 1 vital signs within 1 hour prior to dosing. Vital signs will be monitored every 15 minutes over the 30 minute IV infusion. Vital signs will also be monitored at approximately 30 minutes, 1 hour, and 2 hours (IM or IV infusion) after dosing. If the post-dose monitoring is reduced to 1 hour per JSRT recommendation: Record Day 1 vital signs within 1 hour prior to dosing. Vital signs will be monitored every 15 minutes over the 30 minute IV infusion. Vital signs will also be monitored at approximately 30 minutes and 1 hour after dosing (IM or IV infusion).
7. At Screening, triplicate ECGs will be performed. A single 12-lead ECG will be performed prior to dosing on Day 1, within 30 minutes of end of dosing on Day 1, and on Day 8. If Screening and dosing occur on the same day, only the one set of triplicate ECGs is required prior to dosing (an additional pre-dosing single ECG is not required). Additional ECGs will be done as clinically needed.
8. On Day 1, local injection site tolerability assessment will be performed at approximately 1 hour and 2 hours post-dose. If JSRT recommends reducing monitoring time, Day 1 assessment will be 1 hour post-dose. All injection site reactions need to be followed by the principal investigator (PI) to resolution.
9. On Day 1, sample collection will occur pre-dose. Screening/Day 1 hematology, coagulation, chemistry, and urinalysis only need to be performed once if Screening and dosing occur on the same day. For IM administration, the results of hematology and coagulation laboratory results must be received and reviewed prior to dosing (see exclusion criteria number 11). A list of protocol-required safety laboratory tests is provided in Section 10.2.
10. For women of child-bearing potential (defined in Section 10.4.1): serum or highly sensitive urine pregnancy test, as required by local guidelines (Section 8.5.6).
11. Documentation of laboratory-confirmed SARS-CoV-2 infection via any validated qRT-PCR or other nucleic acid amplification test (NAAT) from any respiratory specimen collected ≤7 days prior to study entry must be confirmed at Screening. If not available, or previous qRT-PCR test was negative, a SARS-CoV-2 qRT-PCR or other NAAT must be performed at Screening to confirm eligibility.
12. Day 1 samples will also be evaluated for SARS-CoV-2 characterization (e.g., identification of variants).
13. On Day 1, Cohort A participants will have a single PK sample collected at the end of infusion. Cohort B participants will not have any PK samples collected on Day 1.
14. Day 1 sample collection is pre-dose only.
15. AEs (Section 10.3), including MIS-C, will be collected until Week 36 (EOS) during site visits and phone calls.
16. All SAEs (Section 10.3) will be collected from dose administration and only SAEs considered related to study participation or a GSK product will be collected from signing informed consent. SAEs will be collected during all site visits and phone calls. Note: all SAEs must be reported within 24 hours.

## Table 2 SoA for Participant <2 Years of Age

| | Study Visit Day ± Visit Window | Screening[1] (Day -2, -1, or 1) | Day 1[1] | Day 3` | Day 5 | Day 8 | Day 11 | Day 14 | Day 22 | Day 29 ± 3d | Week 12 (Day 85 ± 7d) | Week 36 (Day 252 ± 14d) End of study (EOS) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Clinic (C) or home (H) visit | C | C | C/H | C/H | C/H | C/H | C/H | C/H | C/H | C/H | C/H |
| | Informed consent | X | | | | | | | | | | |
| | Demography | X | | | | | | | | | | |
| | Medical history (including baseline COVID-19 symptoms and comorbidities) | X | | | | | | | | | | |
| | Eligibility criteria | X | | | | | | | | | | |
| | Study intervention administration | | X[2] | | | | | | | | | |
| Assessments | Physical examination (F=full, B=brief) | F[3] | F[3] | | | B | | B | B | B | | |
| Assessments | COVID-19 signs/symptoms review | X | X | | | X | | X | | X | X | X |
| Assessments | Monitoring of COVID-19 disease progression | | <----------X (Daily)[4]----------> | | | | | | X | X | | |
| Assessments | Phone call for subsequent COVID-19 monitoring | | | | | | | | | | Weekly from Week 5 to Week 11[5] | Weekly from Week 13 to Week 35[5] |
| Assessments | Vital signs (including blood pressure, pulse rate, respiratory rate, temperature, and oxygen saturation) | X | X[6] | X | X | X | | X | X | X | X | X |
| Assessments | 12-lead ECG[7] | X[7] | X[7] | | | X | | | | | | |
| Assessments | Local injection site tolerability assessment (IM only)[8] | | X[8] | X | X | X | | | | | | |
| Sample collection | Urine studies | X[9] | X[9] | | | X | | | | X | | |
| Sample collection | Hematology and chemistry studies | X[9] | X[9] | | | X | | X | | X | | |
| Sample collection | Coagulation studies | X[9] | X[9] | | | | | | | | | |
| Sample collection | SARS-CoV-2 diagnostic test (if not previously confirmed, point-of-care or local laboratory test) | X[10] | | | | | | | | | | |
| Sample collection | Nasal mid-turbinate swab for virology and resistance analyses | | X[11, 13] | X | X | X | X | | | X | | |
| Sample collection | Blood sample for PK analysis | | X[12] | | X | | | | | X | X | |
| Sample collection | Blood sample for anti-drug antibody | | X[13] | | | | | | | X | | X |
| | AE review[14] | | <---------- X ----------> | | | | | | | | | |
| | SAE review[15] | X[15] | <---------- X ----------> | | | | | | | | | |
| | Concomitant medication review | <---------- X ----------> | | | | | | | | | | |

**Notes:** In case of early discontinuation (ED) or withdrawal (EW), all Week 36 activities should be performed.

1. All Screening procedures must be completed within 2 days prior to dosing. When possible, Screening and dosing (Day 1) can be done on the same day. Contact information for secondary contacts will be collected at Screening and information about health care providers/facilities may also be collected at Screening.
2. Dosing will be performed ≤7 days from the onset of symptoms. Participants will be monitored for 2 hours after dosing. If the Joint Safety Review Team (JSRT) recommends reducing to 1 hour monitoring (see Section 10.1.5.1): Participants will be monitored for approximately 1 hour post-dose.
3. Including height, weight, and body mass index (BMI). The full physical examination only needs to be performed once if Screening and dosing occur on the same day.
4. Daily assessment will be via a phone call when a clinic or home visit is not scheduled.
5. Weekly phone call from Week 5 to Week 11 and Week 13 to Week 35 to assess for the incidence and severity of subsequent COVID-19 illness, if any. Weekly assessments must be performed within ±1 day of the scheduled phone call.
6. Record Day 1 vital signs within 1 hour prior to dosing. Vital signs will be monitored every 15 minutes over the 30 minute IV infusion. Vital signs will also be monitored at approximately 30 minutes, 1 hour, and 2 hours (IM or IV infusion) after dosing. If the post-dose monitoring is reduced to 1 hour per JSRT recommendation: Record Day 1 vital signs within 1 hour prior to dosing. Vital signs will be monitored every 15 minutes over the 30 minute IV infusion. Vital signs will also be monitored at approximately 30 minutes and 1 hour after dosing (IM or IV infusion).
7. At Screening, triplicate ECGs will be performed. A single 12-lead ECG will be performed prior to dosing on Day 1, within 30 minutes of end of dosing on Day 1, and on Day 8. If Screening and dosing occur on the same day, only the one set of triplicate ECGs is required prior to dosing (an additional pre-dosing single ECG is not required). Additional ECGs will be done as clinically needed.
8. On Day 1, local injection site tolerability assessment will be performed at approximately 1 hour and 2 hours post-dose. If JSRT recommends reducing monitoring time, Day 1 assessment will be 1 hour post-dose. All injection site reactions need to be followed by the principal investigator (PI) to resolution.
9. On Day 1, sample collection will occur pre-dose. Screening/Day 1 hematology, coagulation, chemistry, and urinalysis only need to be performed once if Screening and dosing occur on the same day. For IM administration the results of hematology and coagulation laboratory results must be received and reviewed prior to dosing (see exclusion criteria number 11). A list of protocol-required safety laboratory tests is provided in Section 10.2.
10. Documentation of laboratory-confirmed SARS-CoV-2 infection via any validated qRT-PCR or other nucleic acid amplification test (NAAT) from any respiratory specimen collected ≤7 days prior to study entry must be confirmed at Screening. If not available, or previous qRT-PCR test was negative, a SARS-CoV-2 qRT-PCR or other NAAT must be performed at Screening to confirm eligibility.
11. Day 1 samples will also be evaluated for SARS-CoV-2 characterization (e.g., identification of variants).
12. On Day 1, Cohort A participants will have a single PK sample collected at the end of infusion. Cohort B participants will not have any PK samples collected on Day 1.
13. Day 1 sample collection is pre-dose only.
14. AEs (Section 10.3) including MIS-C will be collected until Week 36 (EOS) during site visits and phone calls.
15. All SAEs (Section 10.3) will be collected from dose administration and only SAEs considered related to study participation or a GSK product will be collected from signing informed consent. SAEs will be collected during all site visits and phone calls. Note: all SAEs must be reported within 24 hours.

# 2. INTRODUCTION

## 2.1. Study Rationale

There is an urgent medical need for therapeutics for the treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19). Early treatment of mild and moderate disease in outpatients could prevent the more severe sequelae of COVID-19 requiring hospitalization, such as respiratory failure, and non-respiratory complications of COVID-19 including thromboembolic disease leading to pulmonary embolism and stroke, myocardial injury and arrhythmias, renal failure, and shock, among others [Klok, 2020; Chen, 2020; CDC COVID-19 Response Team, 2020]. Furthermore, a potent treatment given early in disease could ameliorate the severity and duration of COVID-19 and potentially reduce transmission.

Throughout the COVID-19 pandemic, a number of risk factors have come to be associated with worse clinical disease in adults: advanced age and patients with comorbidities such as obesity, diabetes, hypertension, chronic kidney disease, and congestive heart failure were more likely to have severe disease requiring hospitalization or die [Booth, 2021; Rosenthal, 2020; Williamson, 2020; Richardson, 2020; Garg, 2020; Petrilli, 2020]. While children are more likely than adults to have asymptomatic or mild infection, they account for more than 14% of total cases since the pandemic began and comprise 19% of all new COVID-19 cases for the week ending on 10 June 2021 [AAP, 2021] and significant morbidity and mortality can also be seen during acute infection. Between 04 January 2021 and 20 June 2021, approximately 15.8% of 4.79 million COVID-19 cases reported in the European Economic Area (EEA), excluding the United Kingdom (UK), were in children (those aged 18 years and under) [ECDC, 2021]. Children have comprised an increasing proportion of weekly COVID-19 case numbers since January 2021, with the largest increase among those aged 5 to 11 years. This increasing proportion of weekly cases in children corresponds with the start of vaccination rollout in the European Union (EU)/EEA [ECDC, 2021]**.** Pediatric patients with COVID-19 are more likely to be hospitalized with severe disease or die if they are young (≤1 year) or have a history of obesity, gastrointestinal conditions, congenital heart disease, genetic or metabolic conditions, neurologic disease, diabetes mellitus, asthma or chronic lung disease, immunosuppression, sickle cell disease, or baseline medical complexity [CDC, 2021c; Graff, 2021; Kim, 2020]. Furthermore, multisystem inflammatory syndrome in children (MIS-C) represents a rare complication of SARS-CoV-2 infection observed in children and recently a similar syndrome in adults, multisystem inflammatory syndrome in adults (MIS-A), has also been observed [Feldstein, 2020; Morris, 2020]. Multisystem inflammatory syndrome in children generally presents between 2 to 6 weeks following SARS-CoV-2 infection, suggesting a post-infectious complication potentially driven by formation of pathogenic autoantibodies [Gottlieb, 2021; Consiglio, 2020; Gruber, 2020].

Although severe COVID-19 in any age group puts strain on healthcare systems, severe COVID-19 in a pediatric population can be particularly problematic in the absence of local or regional hospitals equipped to treat severely ill children [Levin, 2021].

For early treatment of non-hospitalized pediatric patients with mild-to-moderate COVID-19 at high risk of progression to severe disease, the monoclonal antibody (mAb) combinations of bamlanivimab/etesevimab and casirivimab/imdevimab have been authorized (Emergency Use Authorization [EUA]) in adolescents aged 12 to 18 years (≥40 kilograms [kg]) for prevention of disease progression [EMA, 2021; FDA, 2021d; FDA, 2020c; Roche, 2021]. However, on 25 June 2021, the Department of Health and Human Services (HHS) halted the distribution of bamlanivimab/etesevimab in the United States of America (US) due to their lack of activity against the Gamma variant (Brazil) and the Beta variant (South Africa) [Eli Lilly and Company, 2021].

Other treatments including remdesivir, baricitinib, remdesivir/baricitinib, and dexamethasone (off-label use) in children are exclusively recommended for severe or critical COVID-19 [NIH, 2021; REACT, 2020; FDA, 2021b; RECOVERY, 2021].

There are no other treatment options approved for children, none for children below the age of 12 years with mild-to-moderate COVID-19, and none for children under the age of 2 years with severe disease. Further, the route of administration for existing mAb combinations is intravenous (IV) with 20 to 70 minute infusion times for outpatients at a time when patients are still infectious and access to facilities for IV administration has been a rate-limiting step [National Academies of Sciences, Engineering, and Medicine, 2021]. Given the time required for infusion of other authorized mAbs and the limited outpatient availability of sites for infusion, strategies that allow for treatment at pharmacies, primary care clinics, and other point-of-diagnosis sites will unburden the healthcare system and offer the opportunity to reach more pediatric patients—especially in sites that do not have pediatric specialty care.

Therefore, there is an urgent need for the development of new treatment modalities with an accessible administration route (intramuscular [IM]) and preserved activity against emerging SARS-CoV-2 variants.

Vir Biotechnology, Inc. (Vir) has developed a human neutralizing anti-SARS-CoV-2 antibody, VIR-7831 (GSK4182136, hereafter referred to as sotrovimab), which has an Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life ($t_{1/2}$) [Pinto, 2020]. In humans, sotrovimab has a $t_{1/2}$=48.8 days. Sotrovimab binds with high affinity to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. Vir Biotechnology, Inc and GlaxoSmithKline (GSK) are collaborating on the development of sotrovimab for the treatment of COVID-19, including the use of sotrovimab via IV infusion and IM injection.

Sotrovimab (500 mg, IV) was assessed in participants with COVID-19 in an early treatment study, VIR-7831-5001 (GSK Study 214367, also known as COMET-ICE [NCT04545060]), with the aim of preventing disease progression in non-hospitalized participants. For the first planned interim analysis, the Independent Data Monitoring Committee (IDMC) met on 10 March 2021 and reviewed data from 583 participants. The IDMC recommended halting enrollment in the trial due to overwhelming efficacy, with an 85% reduction in the risk of hospitalization or death in the sotrovimab arm versus the placebo arm (primary endpoint) [Vir Biotechnology, 2021]. The results of this study supported the Emergency Authorization submissions. Emergency authorizations and/or

marketing approvals for sotrovimab (Gen2) for the treatment of mild-to-moderate COVID-19 have been received in the US on 26 May 2021 (EUA) [FDA, 2021e], positive opinion via Article 5(3) in the EU on 20 May 2021, Canada on 30 July 2021 (Interim Order), Singapore on 30 June 2021 (Pandemic Special Access), Italy on 29 July 2021 (Temporary Authorization) and Australia on 20 August 2021 (Provisional Marketing Authorization). Similar emergency use applications have also been approved in the United Arab Emirates, Bahrain, Kuwait, Qatar, Oman, Switzerland, Egypt, Brazil, and a conditional marketing approval in Saudi Arabia.

Sotrovimab has been formulated to allow for either IV or IM administration. Administration via IM dosing could allow greater access to mAb treatment without the requirement of facilities for IV administration. The IM administration is currently being evaluated in a study to evaluate safety, tolerability, pharmacokinetics (PK), and viral pharmacodynamics (PD) of sotrovimab administered intravenously or via IM injection in participants with mild to moderate COVID-19 (VIR-7831-5006/GSK Study 216912, also known as COMET-PEAK; NCT04779879) and in a Phase 3 study (COMET-TAIL [VIR-7831-5008/GSK Study 217114; NCT04913675]) to assess the efficacy, safety, and tolerability of sotrovimab given IM versus IV for the treatment of mild/moderate COVID-19 in high-risk non-hospitalized participants. The COMET-TAIL study is evaluating the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab for the prevention of progression of COVID-19 in a non-inferiority setting and includes enrollment of adolescent participants between the age of 12 to 17 years.

Sotrovimab is a dual action mAb derived from the parent antibody S309 identified from a 2003 SARS-CoV survivor. It targets a highly conserved epitope in the region of the spike RBD that does not compete with angiotensin converting enzyme 2 (ACE2) binding and is outside of the receptor-binding motif (RBM) [Pinto, 2020]. Furthermore, this epitope does not overlap with mutations in current variants of concern and continues to be highly conserved; additionally, sotrovimab has a high barrier to resistance observed *in vitro* [Starr, 2021; Wang, 2021].

Pseudotyped virus-like particle *in vitro* assessments indicate that sotrovimab retains activity against the UK (Alpha, B.1.1.7; 2.30-fold change in $EC_{50}$ value); South Africa (Beta, B.1.351; 0.60-fold change in $EC_{50}$ value); Brazil (Gamma, P.1; 0.35-fold change in $EC_{50}$ value); California (Epsilon, B.1.427/B.1.429; 0.70-fold change in $EC_{50}$ value); New York (Iota, B.1.526; 0.6-fold change in $EC_{50}$ value), India (Kappa, B.1.617.1; 0.7-fold change in $EC_{50}$ value, Delta, B.1.617.2; 1-fold changed in $EC_{50}$ value, Delta Plus [AY.1; 1.1-fold change in $EC_{50}$ value and AY.2; 1.3-fold change in $EC_{50}$ value]) and Peru (Lambda, C.37; 1.5-fold change in $EC_{50}$ value) variant spike proteins. Microneutralization data from authentic SARS-CoV-2 variant virus also indicate that sotrovimab retains activity against the UK (3-fold change in $EC_{50}$ value), South Africa (1.2-fold change in $EC_{50}$ value) and Brazil (1.6-fold change in $EC_{50}$ value) variants.

This study will evaluate the PK, safety, and PD of sotrovimab administered IM or IV in children from birth to less than 18 years old with mild-to-moderate COVID-19 at high risk of disease progression.

## 2.2. Background

In December 2019, an atypical pneumonia caused by a novel coronavirus SARS-CoV-2 was first reported in Wuhan, China and has subsequently spread rapidly around the world. As of 17 June 2021, 177,156,095 cases of COVID-19 have been reported, including 3,835,309 associated deaths [Johns Hopkins, 2021]. The first recorded case in the US was reported on 20 January 2020 in the Pacific North-western area of the country [Holshue, 2020]; as of 15 June 2021, over 33 million cases have been reported with over 500,000 associated deaths in the US [CDC, 2021a].

As of 17 June 2021, children <18 years of age accounted for 12.5% of reported COVID-19 cases in the US [CDC, 2021b]. The incidence of laboratory confirmed COVID-19 in the pediatric population is age-dependent. Average weekly incidence from May to September 2020 among adolescents aged 12 to 17 years of age was almost double that of the incidence among children aged 5 to 11 years (37.4 per 100,000 children compared to 19.0 per 100,000 children) [Leeb, 2020].

Children generally have a good prognosis and recover within 1 to 2 weeks after symptom onset [Cavallo, 2020; Ludvigsson, 2020]. However, among children who have been hospitalized with COVID-19, the most common co-morbidities are obesity, chronic lung disease, asthma, and prematurity (<37 weeks gestational age at birth) [Kim, 2020]. Apart from several mAb combinations authorized only in adolescents and available only via IV infusion, there are no other authorized treatment option in children specifically in those at high risk of disease progression. Therefore, development of additional treatment modalities that have a more accessible administration route and preserved activity against emerging SARS-CoV-2 variants are warranted for the treatment of COVID-19 in children.

Vir Biotechnology, Inc. has developed a human neutralizing anti-SARS-CoV-2 antibody, sotrovimab, which has an Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase $t_{1/2}$ [Pinto, 2020]. Sotrovimab binds with high affinity to the RBD of the SARS-CoV-2 spike protein, retains its activity against SARS-CoV-2 variants of concerns, and displays a high barrier to resistance.

### 2.2.1. Clinical Experience with Sotrovimab

As of 31 March 2021, approximately 1350 participants have been randomized to either sotrovimab (500 mg dose) or placebo in two clinical studies: 1057 participants in a study evaluating sotrovimab for the treatment of non-hospitalized individuals with mild to moderate COVID-19 (COMET-ICE [NCT04545060]) and 300 participants in a study that evaluated sotrovimab for the treatment of individuals hospitalized with COVID-19 (ACTIV-3-TICO [VIR-7831-5004; GSK Study 215149; NCT04501978]).

COMET-ICE, is a seamless first-in-human (FIH) Phase II/III study assessing the safety and efficacy of a single 500 mg IV dose of sotrovimab for the early treatment of COVID-19 in non-hospitalized participants at high risk for progression and subsequent hospitalization. Participants were randomized in a 1:1 ratio to sotrovimab or placebo. COMET-ICE started with a lead-in phase (N=21) in August 2020 to assess safety and tolerability. An IDMC met 23 September 2020 to review unblinded safety data after the

20th participant from the lead-in cohort completed Day 15 (1 participant was withdrawn). There were no deaths or SAEs reported up to this IDMC review. The IDMC recommended the study to proceed with the expansion-phase to enroll additional participants across each treatment group (~1300 participants total).

The IDMC subsequently met on 10 March 2021 for a planned interim analysis, with review of data from 583 participants. There was an 85% reduction in the primary endpoint of hospitalization or death in the sotrovimab arm versus the placebo arm (p=0.002). The IDMC recommended that the study halt enrollment on the basis of overwhelming efficacy [Vir Biotechnology, 2021]. There have been no safety concerns identified at the IDMC reviews conducted to date.

Enrolment into COMET-ICE was closed on 11 March 2021, participants continue to be followed-up to Week 24. Results from the COMET-ICE study at the Day 29 Analysis data cut-off (DCO; 27 April 2021) indicate that sotrovimab is a highly efficacious treatment for participants with mild-to-moderate COVID-19 who are at risk of progressing to severe disease, meeting an unmet medical need. A review of COMET-ICE efficacy data based on the intent-to-treat (Day 29) population (N=1057) who received either sotrovimab or placebo demonstrated that the primary efficacy endpoint was met. Treatment with sotrovimab resulted in a significant reduction in the proportion of participants with mild/moderate COVID-19 progressing to greater than 24 hours hospitalization or death in the sotrovimab arm when compared with placebo through Day 29 by 79% (adjusted relative risk reduction; p<0.001).

*In vitro* neutralization data using a SARS-CoV-2 pseudotyped virus are currently available for 13 of the 17 unique variants detected in the sotrovimab epitope. Of the variants with available data, sotrovimab effectively neutralized epitope variants at most amino acid positions tested with fold changes in half maximal effective concentration ($EC_{50}$) <3-fold (range: 0.70 to 1.72). The variants E340A and E340K resulted in significant $EC_{50}$ shifts (>100-fold) indicating reduced susceptibility to sotrovimab *in vitro*.

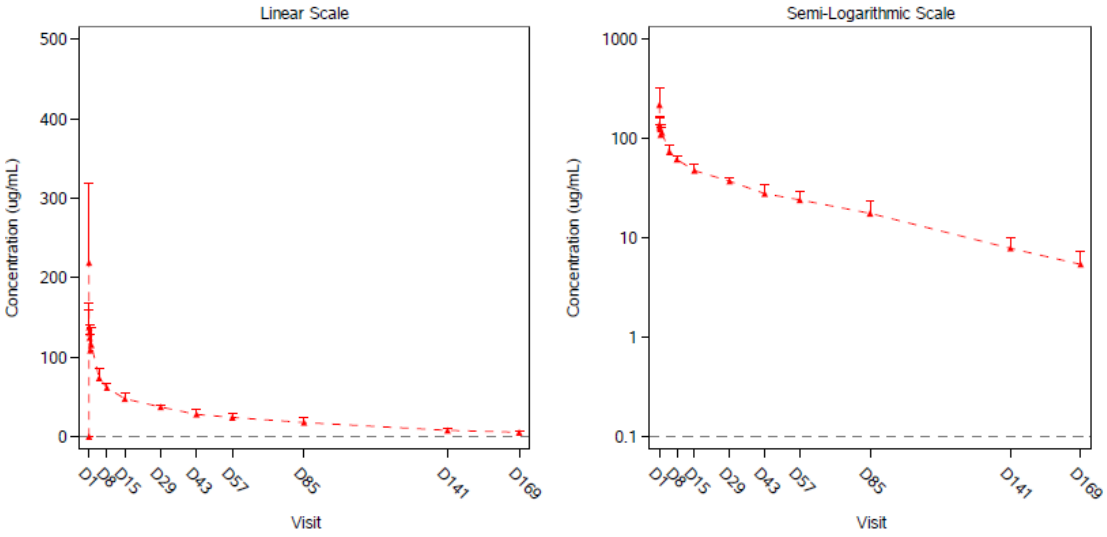
Limited nucleotide sequencing data from a total of 539 COMET-ICE participants indicated that 36 participants (16 treated with placebo and 20 treated with sotrovimab) carried the B.1.1.7 (Alpha, UK origin) variant. Four participants (2 treated with placebo and 2 treated with sotrovimab) carried the N501Y substitution. Thirty-one participants (19 treated with placebo and 12 treated with sotrovimab) carried the B.1.427/B.1.429 (Epsilon, California origin) variant. Eight additional participants carried the L452R substitution (6 treated with placebo and 2 treated with sotrovimab). Eleven participants carried the P.1 (Gamma, Brazil origin) variant (3 treated with placebo and 8 treated with sotrovimab). Three participants carried the B.1.526 (Iota, New York origin) variant with the E484K substitution (2 treated with placebo and 1 treated with sotrovimab), while 9 participants (4 treated with placebo and 5 treated with sotrovimab) carried the S477N substitution that has been associated with the B.1.526 (Iota, New York origin) variant. Additionally, 10 participants carried the E484K substitution (4 treated with placebo and 6 treated with sotrovimab), 2 carried the S494P substitution (1 treated with placebo and 1 treated with sotrovimab), and 3 carried the S494P substitution with the N501Y substitution (2 treated with placebo and 1 treated with sotrovimab). Two participants in

the group receiving sotrovimab (1 carrying the B.1.427/B.1.429 [Epsilon, California origin] variant and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. Four participants in the placebo group (2 carrying the E484K substitution, 1 carrying the P.1 [Gamma, Brazil origin] variant, and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. None of the participants with currently available baseline sequences carried the full complement of substitutions characteristic of the B.1.351 (Beta, South Africa origin) or B.1.617 (Delta, India origin) variants.

The PK of a 500 mg IV dose of sotrovimab administered via a 1 hour IV infusion was evaluated in COMET-ICE. There were 10 participants in the sotrovimab arm in the Lead-in Phase of this study. One participant discontinued early due to withdrawal of consent following infusion with sotrovimab. Complete serum PK from 9 participants (sotrovimab) in the Lead-in phase of COMET-ICE is therefore available. The mean maximum observed concentration ($C_{max}$) of 500 mg sotrovimab was 219 µg/mL following a 1 hour IV infusion. The mean serum level on Day 29 is 37.2 µg/mL. The mean clearance (CL) and volume of distribution at steady state ($V_{ss}$) were 125 mL/day and 8.1 L, respectively. The median half-life was 48.8 days. The mean PK profile and parameters are presented in Figure 1 and Table 3.

Partial sparse serum PK through study Day 29 from 363 participants in the COMET-ICE Expansion phase is available to date. The mean serum concentration of sotrovimab on study Day 29 is 25.8 µg/mL.

**Figure 1 Mean (+ standard deviation [SD]) Sotrovimab Serum Concentration-Time Plots (Linear and Semi-log): COMET-ICE Lead-In Phase**




Note: Lower limit of quantification (LLQ)=0.1 µg/mL. Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist.
Data is based on 1-hour infusion time.

**Table 3 Sotrovimab PK Parameters Following a 500 mg IV Dose: COMET-ICE Lead-in Phase**

| Parameter | Dose 500 mg (N = 9[a]) |
|---|---|
| $C_{max}$, µg/mL | 219 (45.5) |
| $T_{max}$, day | 0.04 (0.04, 0.05) |
| $C_{last}$, µg/mL | 5.41 (37.2) |
| $T_{last}$, day | 161 (160, 167) |
| $AUC_{D1-29}$, day*µg/mL | 1529 (9.6) |
| $AUC_{last}$, day*µg/mL | 3714 (14.5) |
| AUC % Extrapolated | 9.4 (37.9) |
| $AUC_{inf}$, day*µg/mL | 4116 (16.9) |
| CL (mL/day) | 125 (17.9) |
| $V_z$, L | 8.76 (15.7) |
| $V_{ss}$, L | 8.1 (11.1) |
| $t_{1/2}$, day | 48.8 (37.8, 59.4) |

Abbreviations: AUC = area under the curve; $AUC_{last}$ = area under the serum concentration-time curve from time zero to time of last measurable concentration; AUC % Extrapolated = area under the plasma concentration-time curve extrapolated from time to infinity as a percentage of total AUC; $AUC_{D1-29}$ = area under the serum concentration-time curve from Day 1 to Day 29; $AUC_{inf}$ = area under the serum concentration-time curve from time zero to infinity; $C_{last}$ = last measurable serum concentration; $C_{max}$ = maximum observed concentration; CL = clearance; $t_{1/2}$ = terminal elimination half-life; $t_{max}$ = time to reach $C_{max}$; $t_{last}$ = time of the last quantifiable concentration; $V_{ss}$ = volume of distribution at steady state; $V_z$ = apparent volume of distribution during terminal phase.

Note: Parameters are reported as mean (%CV) except for $T_{max}$, $T_{last}$, and $t_{1/2}$, which are presented as median (min, max).
Data is based on 1-hour infusion time.

[a] N=8 for $AUC_{D1-29}$ as participant 10016 was missing all PK samples prior to Study Day 5.

Sotrovimab was also studied for the treatment of hospitalized participants with COVID-19 in GSK Study 215149, also known as ACTIV-3-TICO, sponsored by the National Institute of Allergy and Infectious Diseases. The ACTIV-3-TICO study was a randomized, blinded, placebo-controlled platform study that allows investigational drugs to be added and dropped during the course of the study. The sub-study evaluating sotrovimab administered by IV infusion started in December 2020 and aimed to enroll approximately 500 participants per treatment arm.

On 01 March 2021, the Data and Safety Monitoring Board (DSMB) recommended recruitment in the sotrovimab sub-protocol should cease, and follow-up of already randomized participants is ongoing. There were no safety concerns identified by the DSMB [GlaxoSmithKline, 2021b]. One potentially life-threatening allergic reaction (anaphylaxis) was reported during infusion in ACTIV-3-TICO in a participant who received sotrovimab. The time to onset was 21 minutes after the start of infusion and the event was considered related to study treatment. The participant was treated for the allergic reaction and recovered.

Sotrovimab administered by IV infusion is also being evaluated in the BLAZE-4 study (VIR-7831-5007/GSK Study 217079; NCT04634409), a clinical trial with multiple arms evaluating anti-SARS-CoV-2 mAbs from Eli Lilly and Company. One arm compared the

combination of bamlanivimab with sotrovimab to placebo (randomized 1:1) for the treatment of mild to moderate COVID-19. The study has completed enrolment and is currently in the follow-up period. Day 29 topline analysis showed that the study met the primary endpoint (percentage of participants with SARS-CoV-2 viral load greater than log 5.27) and combination treatment was well tolerated with regards to acute infusion-related reactions (IRRs) and there were no safety concerns [GlaxoSmithKline, 2021a].

Sotrovimab 500 mg administered intravenously or via IM injection is also currently being evaluated for the treatment of mild-to-moderate COVID-19 (VIR-7831-5006/GSK Study 216912], also known as COMET-PEAK [NCT04779879]).COMET-PEAK has 3 parts (Part A, Part B, and Part C). COMET-PEAK Parts A, B, and C are fully enrolled. Part A is evaluating safety, tolerability, virology, immunogenicity, and PK in participants that received Generation1 (Gen1) or Generation2 (Gen2) sotrovimab via a 500 mg IV infusion. In Part B and Part C, viral load pharmacodynamics (PD) as assessed via upper respiratory samples, safety, tolerability, immunogenicity, and PK are being evaluated in participants that receive Generation2 sotrovimab via IM injection (500 mg in Part B, 250 mg in Part C) or IV infusion (500 mg in both Part B and Part C).

Data from an initial analysis from COMET-PEAK Part A and B to Day 29, which includes 197 randomized patients, are available. In Part A (safety population N=30; Gen1 500 mg IV: n=8, Gen2 500 mg IV: n=22), there were 3 AEs reported in the Gen2 formulation arm (unrelated to study treatment) and no SAEs were reported. No IRRs were reported in Part A. In Part B (safety population N=166; Gen2 500 mg IV: n=84, Gen2 500 mg IM: n=82), there were 8 (10%) AEs in the 500 mg IV arm and 17 (21%) AEs in the 500 mg IM arm. In total, 5 SAEs, which were all unrelated to study treatment, were reported across both arms in Part B. No sensitivity or IRRs occurred in the Part B 500 mg IV arm. One (1%) participant had a hypersensitivity event and 9 (11%) participants reported injection site pain events in the Part B 500 mg IM arm. For COMET-PEAK results to date, there were no new safety findings that would significantly impact the benefit:risk assessment. The 500 mg IM dose (given as two 4 mL dorsogluteal injections) was also well tolerated.

Sotrovimab is also being evaluated in non-hospitalized participants at high risk for disease progression (VIR-7831-5008/GSK Study 217114 [NCT04913675], also known as COMET-TAIL). The COMET-TAIL study is fully enrolled. COMET-TAIL is a Phase 3 randomized, multi-center, open label study to assess the efficacy, safety, and tolerability of sotrovimab given IM versus IV for the treatment of mild/moderate COVID-19 in high-risk non-hospitalized participants. COMET-TAIL will evaluate the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab in preventing progression of COVID-19 in a non-inferiority setting and will include enrollment of adolescent participants between the age of 12 to 17 years. Following review of available data, the decision was made by COMET-TAIL JSRT and IDMC to permanently discontinue enrollment in the sotrovimab 250 mg IM arm. This decision was made due to an imbalance in the limited number of hospitalizations to date, and no study-wide or other safety concerns were noted at this time.

Additionally, a Phase 1 study is ongoing to evaluate the PK, safety, and tolerability of 500 mg sotrovimab administered IV or IM in healthy Japanese and Caucasian

participants (VIR-7831-5009/GSK Study 217653; NCT04988152). This study started in July 2021 and is fully enrolled. This study has two parts: Part 1 is evaluating IV sotrovimab and Part 2 is evaluating IM sotrovimab. Day 29 safety data for Part 1 is available to date. No SAEs have been reported for Part 1. Two participants in the Part 1 placebo arm reported AEs (1 [33%] Japanese participant and 1 [33%] Caucasian participant) and 3 participants in the Part 1 sotrovimab arm reported AEs (2 [22%] Japanese participants and 1 [11%] Caucasian participant).

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of sotrovimab may be found in the Investigator's Brochure (IB).

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s): Sotrovimab** | | |
| Hypersensitivity reactions (HSRs) | While sotrovimab is a human Immunoglobulin G1 (IgG1) mAb, hypersensitivity is a potential general risk associated with the mAb class of therapeutics.<br><br>There was no evidence of systemic infusion reactions in toxicology studies conducted with sotrovimab in monkeys.<br><br>In COMET-ICE, all hypersensitivity reactions were non-serious, of Grade 1 (mild) or Grade 2 (moderate) severity and reported in 2% of participants who received sotrovimab and in <1% who received placebo (9 participants treated with sotrovimab; 5 participants treated with placebo). None of the reactions in either arm led to pausing or discontinuation of the infusions. All events across both treatment groups were reported as resolved or resolving at the time of DCO.<br><br>No anaphylaxis events were reported in the COMET-ICE study in participants with mild to moderate COVID-19 not requiring hospitalization at study entry.<br><br>A potentially life-threatening allergic reaction (anaphylaxis) was observed in 1 adult participant who received sotrovimab in the study of individuals hospitalized with COVID-19 (the ACTIV-3-TICO study). The anaphylaxis was considered by the | • Participants will be excluded if they have a history of hypersensitivity to any of the constituents present in the investigational product.<br>• Participants will be monitored for 2 hours post-administration of study intervention (including vital signs, see Section 8.5.1). After half of participants are dosed in either Cohort (Cohort A or Cohort B), post-dose monitoring might be reduced to 1 hour per JSRT recommendation within the same Cohort.<br>• Investigational product will be administered in the clinic with staff trained in emergency care and resuscitation procedures and emergency care kit on hand during the study intervention administration and post-therapy observation periods.<br>• The JSRT and IDMC will review the safety data of this study at regular intervals.<br>• General guidance on management of hypersensitivity reactions is provided in Section 10.5.<br>• Refer to Section 8.6.4 for follow up regarding AESI. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | investigator to be related to study treatment. The participant was treated for the allergic reaction and recovered. | |
| Infusion Related Reactions (IRRs) | Infusion related reactions are a potential general risk for biologic therapies with IV administration.<br><br>There was no evidence of infusion reactions in toxicology studies conducted with sotrovimab in monkeys.<br><br>In the ongoing COMET-ICE study in participants with mild/moderate COVID-19 with high risk of progression, IRRs that occurred within 24 hours post infusion (pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion related reaction) were reported in 6 (1%) of participants in the sotrovimab arm and 6 (1%) of participants in the placebo arm. All IRRs were non-serious, and Grade 1 or 2 severity and none led to treatment pausing or discontinuation. In the sotrovimab arm all of the cases of IRRs were considered resolved and in the placebo arm one participant had an event considered not resolved at the time of DCO. | • Participants will be monitored for 2 hours post-administration of study intervention (including vital signs, see Section 8.5.1). After half of participants are dosed in either Cohort (Cohort A or Cohort B), post-dose monitoring might be reduced to 1 hour per JSRT recommendation within the same Cohort.<br>• Infusion time can be extended at the discretion of the Investigator or Sponsor based on infusion-related symptoms or other safety findings.<br>• Investigators are instructed to discontinue IV infusions for participants who develop Grade 3 or 4 infusion reactions using the Division of Acquired Immune-Deficiency syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) Adverse Event grading. See Section 7.1 for discontinuation information. For grading of severity see Section 8.6.3 and Section 10.3.4.<br>• If a participant experiences a Grade 2 IRR, investigators are instructed to pause the infusion. The infusion may subsequently resume at a slower pace of infusion, at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids). See Section 7.1.1.<br>• Investigational product will be administered in the clinic with staff trained in emergency care and resuscitation procedures and emergency care kit on hand during the infusion and post-therapy observation periods.<br>• Refer to Section 8.6.4 for follow up regarding AESI. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | | • The JSRT and IDMC will review safety data of this study at regular intervals. |
| Injection Site Reaction (ISR) | Sotrovimab will be administered via IM injection, which has a potential risk of local injection site reactions.<br><br>In a single dose IM local tolerance study in mini pigs at a dose of 250 mg (4 mL, 62.5 mg/L), no injection site reactions were observed.<br><br>The IM route of administration is being evaluated in the COMET-PEAK study. Injection site reactions (pain and/or tenderness) occurred in 9 out of 82 participants who were included in the safety population for the IM injection. All of the ISRs were Grade 1. One ISR occurred immediately post-dose, and the rest occurred within the first hour post-dose. | • Participants will be monitored for 2 hours after injection. After half of participants are dosed in either Cohort (Cohort A or Cohort B), post-dose monitoring might be reduced to 1 hour per JSRT recommendation within the same Cohort. Refer to the SoA (Section 1.3) for more details, including local tolerability assessments.<br>• Participants who have thrombocytopenia (platelet count <50,000/mm$^3$), bleeding diathesis, or a coagulation disorder or are otherwise not recommended to receive an IM injection cannot be enrolled in Cohort B (which is IM administration only), but can be enrolled in Cohort A (which is IV administration only).<br>• The JSRT and IDMC will review safety data of this study at regular intervals.<br>• General guidance on management of ISRs is provided in Section 10.5.<br>• Refer to Section 8.6.4 for follow up regarding AESI. |
| Immunogenicity | While sotrovimab is a human immunoglobulin G (IgG), the development of anti-drug antibodies (ADA) that have the potential to impact safety and/or efficacy are a potential general risk associated with the mAb class of therapeutics.<br><br>Through Day 29 in the COMET-ICE study, the incidence of treatment-emergent anti-sotrovimab antibody responses has remained low with relatively low titers, with no detectable impact on safety or efficacy. | • This study will include participant follow-up for a period of 36 weeks (approximately 5 half-lives) and includes collection of samples for assessment of ADA and potential impact on PK/PD and safety. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Antibody-Dependent Enhancement (ADE) due to sub-neutralizing levels of sotrovimab enhancing fusion or leading to Fc gamma receptor (FcγR) mediated increased viral uptake and replication with virus production | This is a concern related to the potential for participants with sub-neutralizing mAb levels to experience a higher incidence of infection and/or more severe disease compared to participants with no circulating mAb and/or established protective immunity to SARS-CoV-2.<br><br>ADE associated with Dengue virus serotype 1-4 infections is one of the most widely cited examples in which reinfection with a different serotype can, in a minority of patients, run a more severe course in the setting of limited antibodies generated by prior infection.<br><br>The potential for enhanced disease in this setting is due to increased uptake of virus by FcγR-expressing cells such as macrophages and increased viral replication in these cells. Recent data shows that SARS-CoV-2 does not replicate efficiently in macrophages [Hui, 2020], suggesting minimal to no risk of ADE via this mechanism. While there have been some nonclinical reports demonstrating ADE using mAb directed against specific epitopes in the SARS-CoV-2 spike protein [Li, 2021; Zhou, 2021], there was no evidence of ADE either *in vitro* or *in vivo* in nonclinical studies with sotrovimab. These data are consistent with others demonstrating that SARS-CoV-2 replication was abortive in FcγR expressing cells [Hui, 2020] suggesting minimal to no risk of ADE via this mechanism.<br><br>An IDMC reviewed unblinded clinical safety data from the COMET-ICE study. No safety concerns were identified, and the IDMC recommended to halt enrollment based on overwhelming efficacy. Further, as of the Day 29 DCO for the COMET-ICE study, no events consistent with ADE were observed. | • This study will include participant follow-up for a period of 36 weeks to assess for the potential of enhanced disease in participants who develop SARS-CoV-2 infection in the context of waning sotrovimab levels.<br>• Assessment of disease severity will be performed by the JSRT and IDMC to assess for rates of infection or severe disease above what is clinically expected.<br>• Safety guidelines will be provided in the IDMC Charter (see Section 10.1.5 for more details on the IDMC). |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| ADE due to enhanced disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs | There is the possibility that a large amount of antibody that binds, but does not neutralize, virus in the presence of a high viral load could result in immune complex deposition and complement activation in tissue sites of high viral replication, such as the lungs, vascular endothelia, renal, or cardiovascular (CV) tissue [Hamming, 2004], leading to tissue damage/immune complex disease.<br><br>This is hypothesized to have contributed to inflammation and airway obstruction observed in the small airways of infants who received a formalin-inactivated respiratory syncytial virus (RSV) vaccine [Polack, 2002] and in a few cases of fatal H1N1 influenza infection [Wu, 2010].<br><br>The potential for enhanced disease in this setting may be due to low affinity or cross-reactive antibodies with poor or no neutralizing activity.<br><br>Triggering of cytokine release by antibody-virus-FcγR interactions, although usually highly beneficial due to their direct antiviral effects and immune cell recruitment to control viral spread in tissues, also has the potential to enhance pathologic changes initiated by the viral infection.<br><br>Observational data from 5000 COVID-19 patients treated with convalescent plasma, although not placebo controlled, is suggestive that even polyclonal mixtures of neutralizing and non-neutralizing antibodies can be safely administered [Joyner, 2020].<br><br>Sotrovimab shows potent binding *in vitro* as well as neutralization of pseudovirus and live virus; thus, this risk is deemed to be low. | • In this study, the JSRT and IDMC will monitor for the worsening of COVID-19-related end-organ complications and/or greater than expected incidence of end-organ complications in participants who develop COVID-19.<br>• Safety guidelines will be provided in the IDMC Charter (see Section 10.1.5 for more details on the IDMC).<br>• Additional monitoring in the event a participant develops signs or symptoms of cardiac complications (see Section 8.5.4). |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | An IDMC reviewed unblinded clinical safety data from the COMET-ICE study. No safety concerns were identified, and the IDMC recommended to halt enrollment based on overwhelming efficacy. As of the Day 29 DCO for the COMET-ICE study, no events consistent with ADE were observed. | |

### 2.3.2. Benefit Assessment

While children are more likely than adults to have asymptomatic or mild infection, significant morbidity and mortality can be seen during acute infection, specifically in those at high risk of disease progression. Although mAb combinations including bamlanivimab/etesevimab and casirivimab/imdevimab have an active EUA for adolescents aged 12 to <18 years (weighing at least 40 kg) with mild to moderate COVID-19 [EMA, 2021; FDA, 2020c; Roche, 2021], there are no other treatment options approved for these children. As a result, for outpatients, supportive care and monitoring remain the mainstays of current management. In addition, multiple SARS-CoV-2 variants are circulating globally and development of additional treatment strategies with conserved activity against these variants is desirable. The use of sotrovimab for the treatment of mild-to-moderate COVID-19 has been authorized in several countries as described in Section 2.1).

The following are potential benefits to participants in this study:

- Participants may benefit from thorough health assessments they receive during the course of the study.
- Based on data in adults with mild-to-moderate COVID-19 at high risk of progression to severe disease or death, it is possible that treatment with sotrovimab may decrease the likelihood of a participant progressing from mild-to-moderate COVID-19 to severe disease or death in children as well.
- Participants in this study may benefit in the knowledge that they are contributing to the process of developing new therapies for children in an area of unmet need.

### 2.3.3. Overall Benefit: Risk Conclusion

There is prior clinical experience with sotrovimab in the setting of the adult early treatment of COVID-19 (COMET-ICE, BLAZE-4, COMET-TAIL, and COMET-PEAK) and hospitalized treatment in ACTIV-3-TICO. In the COMET-ICE study, there have been no safety concerns identified at the IDMC reviews conducted to date. One case of anaphylaxis was reported in an adult during sotrovimab infusion in the ACTIV-3-TICO study, which resolved with treatment. The COMET-ICE study was halted by the IDMC based on profound efficacy on the first interim analysis [Vir Biotechnology, 2021]. Overall, based on the available clinical data, sotrovimab provides a significant clinical benefit as a treatment for adults with COVID-19 who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19.

Considering that GSK was granted an EUA for sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg [FDA, 2021e] in several countries, the limited availability of treatment options in children with mild-to-moderate COVID-19, the strength of the preclinical and clinical data for sotrovimab, and the implemented safety monitoring plan for the potential risks, the Sponsor believes that the potential benefit of participation in this study outweigh the risks.

# 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The following intercurrent event applies to all endpoints specified below: use of non-permitted medication as defined in Section 6.8.1.

A treatment policy strategy will be used for the analysis of all endpoints, including all data as collected during the study regardless of occurrence of the intercurrent events.

| Objectives | Endpoints[a] | Other Estimand Attributes |
|---|---|---|
| **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<br>• 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) | Population: PK (all participants in Cohort A/Cohort B who are exposed to study intervention and who had at least 1 non-missing PK assessment [non-quantifiable values will be considered as non-missing values])<br>Summary measure: PK model parameters |
| To evaluate the safety and tolerability of sotrovimab by IV or IM administration | • Incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESI) through Day 29 and Week 36 | Population: Safety (all participants who are exposed to study intervention in Cohort A/Cohort B)<br>Summary measure: Counts and percentages |
| **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<br>*An attended medical visit includes visit to a hospital emergency room for management of illness or hospitalization for acute management of illness | Population: Safety<br>Summary measure: Counts and percentages |

| Objectives | Endpoints[a] | Other Estimand Attributes |
|---|---|---|
| | • Development of severe and/or critical respiratory COVID-19 as manifested by requirement for supplemental oxygen through Day 29*<br><br>*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 | Population: Safety<br><br>Summary measure: Counts and percentages |
| 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 | Population: Virology (all participants who are exposed to study intervention in Cohort A/Cohort B and have a quantifiable SARS-CoV-2 viral load measurement at baseline)<br><br>Summary measure: Arithmetic mean |
| CCI [redacted] | | |
| CCI [redacted] | | |

CCI

Abbreviations: ADA = anti-drug antibodies; AEs = adverse events; AESI = adverse events of special interest; anti-N = anti-nucleocapsid; $AUC_{inf}$ = 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 intervention.

# 4. STUDY DESIGN

## 4.1. Overall Design

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[2] 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:

- 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.

[2] For this study, "enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after Screening.

- 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.

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. Refer to Section 6.3 for additional details regarding dispensation monitoring.

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 (SoA; Section 1.3). 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.

Dosing will be based on weight in each age band (Table 4). 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 (Section 4.3). Because endotoxin specification limits for sotrovimab exceeds allowable levels for infants weighing <1.88 kg, infants <2 kg will be excluded from the study. Intramuscular sotrovimab may be administered in dorsogluteal, anterolateral thigh, or deltoid muscles. The injection site location will be per participant/legally authorized representative (LAR) preference and the clinical discretion of the investigator. Dosing will be performed within 2 days of Screening assessment. Dosing must occur ≤7 days from onset of COVID-19 symptoms. Screening can occur on the same day as dosing. Eligible participants will be treated with a single IM or IV dose of sotrovimab on Day 1.

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. Further information about the IDMC and the JSRT are provided in Section 10.1.5.

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.

## 4.2. Scientific Rationale for Study Design

This study is a non-comparator, multicenter, open-label 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 to moderate COVID-19 at high risk of disease progression. Currently SARS-CoV-2 infection remains an extremely important public health issue, with the current pandemic causing significant morbidity and mortality. Despite the relatively mild presentation and positive prognosis of COVID-19 in children, there are a significant number of children that are infected and progress to severe disease or develop complications requiring hospitalization. Pediatric patients with COVID-19 are more likely to be hospitalized with severe disease or die if they are young (≤1 year) or have a history of obesity, gastrointestinal conditions, congenital heart disease, genetic or metabolic conditions, neurologic disease, diabetes mellitus, asthma or chronic lung disease, immunosuppression, sickle cell disease, or baseline medical complexity [CDC, 2021c; Graff, 2021; Kim, 2020]. Given the potential for severe disease in high-risk children, there is a significant unmet need for a medication that could prevent COVID-19 progression. Therefore, this study will enroll pediatric participants from birth to less than 18 years with mild to moderate COVID-19 at high risk of disease progression.

While there are few data in children on the absolute risk of progression, the existing data in pediatric literature support each of these CDC-designated at-risk categories [CDC, 2021c]. Therefore, CDC criteria were considered to be an appropriate reference source [Dong, 2020; Graff, 2021; Kim, 2020; Shekerdemian, 2020] and the study will use these categories to define the pre-morbid conditions for participants at high risk of disease progression (Section 10.6). As in adults, immunocompromised status is a risk factor in children and they will be eligible for inclusion in this trial [CDC, 2021c]. This study will also recruit participants who have pre-morbid (non-COVID-19 related) oxygen/respiratory support requirements, or pre-morbid medical technology-dependence in addition to some conditions unique or over-represented in children [CDC, 2020; Mulder, 2012; Clark, 2017]. COMET-ICE and the ongoing adolescent/adult sotrovimab studies have greatly increased the safety characterization of the drug, and no unanticipated safety issues have emerged from the clinical program to date.

With no approved or authorized vaccines for age 12 and under, treatment of immunocompromised children and children dependent on medical technologies in this age group presently represent an urgent unmet medical need. Extrapolation of efficacious exposure levels and overall efficacy from the COMET-ICE population to these populations is, on balance, reasonable.

The co-primary objectives of this study are to characterize PK of sotrovimab to support dosing in pediatric participants with mild to moderate COVID-19 and to evaluate safety of sotrovimab in this population. Cohort A and Cohort B will provide data to evaluate safety and to characterize PK across age and weight bands, to support IV and IM dosing in pediatric participants as well as safety.

Cohort B initiation will be contingent upon 1) acceptable PK and safety from adolescents aged 12 to <18 years in cohort A and 2) data from COMET-TAIL supporting the efficacy of IM dosing in adults. The exposure-response relationship has not yet been established for sotrovimab in adults following IM administration. This will be determined after the read-out from the COMET-TAIL study and will be used to support initiation of IM administration and enrollment in Cohort B.

The secondary endpoints include evaluation of disease progression through Day 29 and viral load change from baseline in nasal secretions measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) at Day 5, Day 8, and Day 11. Disease progression is defined by need for attended medical visit or escalation to higher level of medical care or death and development of severe/and or critical COVID-19 as manifested through requirement for supplemental oxygen. This study enrolls participants with mild to moderate COVID-19 at high risk of disease progression; therefore, for participants who require oxygen or respiratory support due to pre-morbid conditions, disease progression is defined as any sustained (>24 hours) increase in the level or method of oxygen support required.

## 4.3. Justification for Dose

Conventional allometric scaling, assuming fixed powers of 0.75 and 1.00 for clearance and volume, respectively, were used to scale preclinical pharmacokinetics from cynomolgus monkey to human, and subsequently adult pharmacokinetic data down to pediatrics. Using data from the COMET-ICE study, the target adult dose of 500 mg IV provides a serum $AUC_{inf}$ of 4116 day*µg/mL (from Lead-in phase, median body weight of 76 kg). This study in adults with mild to moderate COVID-19 at risk of progression demonstrated a clinically and statistically significant reduction in the primary endpoint of hospitalization or death by Day 29 in the sotrovimab arm vs placebo without any major safety concerns, and hence represents an appropriate serum exposure target. Although body weight was confirmed as a covariate of sotrovimab exposure, dose adjustment in adults for this or other covariates is not necessary.

Using National Health and Nutrition examination Survey (NHANES)- and World Health Organization (WHO)- validated weight-for-age simulations of various age bands (including conventional WHO bands), doses and dose ratios to adult were selected based on balancing; i) target AUC exposure across each age band, ii) pragmatism in delivery of formulation (multiples of 1 mL for IM injection) and iii) intended dose of excipients (including endotoxin). No dose adjustment for absolute IM bioavailability is required due to the age of the study participants, lower BMI and conservatively chosen adult efficacious dose (i.e., 10x tissue-adjusted $IC_{90}$ upper bound of the 95% CI at 28 days post-dose).

The dosing scheme is shown in Table 4.

**Table 4 Sotrovimab Dosage per Weight**

| 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 |

| Age | Weight Band | Dose (mg) | Volume (mL) |
|---|---|---|---|
| 2 to <6 years | 5 to <15 kg<br>15 to <40 kg | 125<br>250 | 2<br>4 |
| 6 to <12 years | 15 to <40 kg<br>≥40 kg | 250<br>500 | 4<br>8 |
| 12 to <18 years | 15 to <40 kg<br>≥40 kg | 250<br>500 | 4<br>8 |

Intravenous sotrovimab will be administered undiluted using a syringe pump for participants <15 kg, and diluted in 40 mL saline for participants ≥15 kg. Because endotoxin specification limits for sotrovimab exceeds allowable levels for infants weighing <1.88 kg, infants <2 kg will be excluded from the study. Intramuscular injections will be administered without any saline dilution.

All doses can be accommodated by the current drug product presentation. The presentation is a 10R vial containing 500 mg of sotrovimab at a concentration of 62.5 mg/mL active ingredient.

For participants receiving undiluted IV sotrovimab (Section 6.1), the appropriate quantity will be removed from the drug product vial and administered IV via an infusion syringe pump within 30 minutes from the start of administration. For participants receiving diluted intravenous sotrovimab, the appropriate quantity will be removed from the drug product vial and injected into an IV bag and administered by IV infusion within 30 minutes from the start of administration. The need for appropriate pediatric dosing volumes, especially for neonates, will be taken into account once pediatric doses are confirmed.

### 4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

A participant is considered to have completed the study if he/she completes the Week 36 visit.

## 5. STUDY POPULATION

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

### 5.1. Inclusion Criteria

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

**Age**

1. Participant must be 32 weeks estimated gestational age (EGA), day of life (DOL) 0 to <18 years of age inclusive, at either the time of participant's signed assent (if age-appropriate) or parent(s)/legally authorized representative signing the informed consent.

**Type of Participant and Disease Characteristics**

2. Participants with mild-moderate COVID-19, as defined by:

   - A positive SARS-CoV-2 test result by any validated qRT-PCR or other nucleic acid amplification test (NAAT) [FDA, 2021a]

     AND

   - SpO2 ≥94% on room air*

     AND

   - Have one or more of the following symptoms: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhea, shortness of breath, poor appetite or poor feeding, nasal congestion/runny nose, lethargy

     AND

   - Less than or equal to 7 days from onset of symptoms to dosing day (Day 1).

*Note: Some participants may be on baseline oxygen supplementation or respiratory support (CPAP, BiPAP, or ventilator-dependence) prior to contracting COVID-19. Others, such as participants with some unrepaired congenital heart disease, may have baseline $SPO_2$ that is <94% on room air prior to contracting COVID-19. If a participant can maintain his/her baseline $SpO_2$ while on his/her baseline oxygen supplementation (including room air) and baseline respiratory support (modality, pressures, and frequency of use), he/she may be included in the study.

3. Participants at risk of disease progression with at least one of the following criteria (suggested diagnoses for categories are included in Section 10.6):

   - Age <1 year
   - Diabetes mellitus
   - Genetic or metabolic diseases
   - Obesity (as defined as body mass index ($kg/m^2$) ≥95th percentile for age and sex based on local growth charts for children ≥2 years of age [or if not available based on the CDC or WHO growth charts in Section 10.7 and Section 10.8, respectively])
   - Cardiovascular disease
   - Sickle cell disease
   - Pulmonary disease
   - Neurologic disease
   - Immunosuppressed (due to certain medical conditions or being on medications that weaken the immune system

  - Use of systemic corticosteroids is included as defined by dose ≥0.5 mg/kg/day or ≥20 mg/day prednisone equivalents (whichever dose is the lower of the two) taken for ≥2 weeks
- Baseline medical complexity (gastrostomy- or jejunostomy-dependence, parenteral nutrition dependence, tracheostomy-dependence, baseline oxygen requirement, use of CPAP/BiPAP/ventilator support).

**Weight**

4. Body weight with the range stated below:
   - Preterm newborn infants and term newborn infants: ≥2 kg
   - Children 2 years to <18 years:
     - Body mass index (BMI) ≥5$^{th}$ percentile for age based on local growth charts (or if not available based on the CDC or WHO growth charts in Section 10.7 and Section 10.8, respectively).

**Sex and Contraceptive/Barrier Requirements**

5. Male and/or female (according to their reproductive organs and functions assigned by chromosomal complement) [FDA, 2016].
   - Contraception and barriers as well as pregnancy testing is required for females only, as appropriate for the age and sexual activity of pediatric participants and as required by local regulations regarding the methods of contraception for those participating in clinical studies.
   - A female participant is eligible to participate if she is not breastfeeding and is either:
     - Premenarcheal or
     - Not pregnant as confirmed by a negative pregnancy test (serum or highly sensitive urine as required by local regulations) at Screening, before the first dose of study intervention, if of reproductive potential.
       - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
       - See Section 8.5.6 for additional requirements for pregnancy testing during the study participation.

   Women of childbearing potential (WOCBP; as defined in Section 10.4.1) must commit to using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least 36 weeks after the last dose of study intervention. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.

**Informed Consent and Assent**

6. The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian (as defined in Section 10.1.3) and the participant's assent, when applicable, before any study-specific activity is performed (unless a waiver of informed consent has been granted by an Institutional Review Board [IRB]/Ethics Committee [EC]). All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand.
7. The participant capable of providing signed and dated written assent signs and dates a written assent form (age appropriate) and the parent/guardian signs and dates a written informed consent form (ICF) for study participation prior to the initiation of any study-related activities. Informed consent is described in Section 10.1.3.

**Other**

8. A legal guardian or primary caregiver must be available to help the study-site personnel ensure follow-up; support the participant to attended assessment days according to the SoA (e.g., able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed.
9. A legal guardian or primary caregiver must be able to accurately maintain the child's take-home record, including items of general health.

## 5.2. Exclusion Criteria

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

**Medical Conditions**

1. Pregnant or breastfeeding.
2. Currently hospitalized, or judged by the investigator as likely to require hospitalization in the next 24 hours, due to severe or critical COVID-19.

Note: If the infant has been hospitalized due to other reasons (e.g., prematurity) or will be hospitalized for reason of administering the study treatment then they can be included in the study.

3. Respiratory rate:
   - 0-6 months: >60 breaths/minute (min)
   - 6 months to 5 years: >30 breaths/min
   - 6 years to <18 years: >20 breaths/min
4. Shortness of breath at rest or respiratory distress.
5. Shock (septic, neurogenic, anaphylactic, cardiogenic, or hypovolemic shock; systemic inflammatory response syndrome).
6. Multiorgan dysfunction.
7. Participants who, in the judgement of the investigator are likely to die in the next 7 days.
8. Multisystem inflammatory syndrome in children (MIS-C) [CDC HAN, 2020], defined as a participant:
   a. Participants presenting with fever ≥38°C, laboratory evidence of inflammation (such as elevated C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid, lactate dehydrogenase [LDH], interleukin 6 [IL-6], neutrophilia, lymphopenia or hypoalbuminemia) and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);

AND

   b. No alternative plausible diagnoses;

AND

   c. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.
9. Post-conceptional age less than 32 completed weeks at time of Screening.
10. History of sudden infant death or unexplained death in a sibling.
11. For Cohort B only: Participant has any condition that would prohibit receipt of IM injections in the investigator's opinion such as coagulation disorder, bleeding diathesis, or thrombocytopenia (platelet count <50,000/$mm^3$).

**Prior/Concomitant Therapy**

12. Prior, current, or planned future use of any of the following treatments during the study period: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (e.g., casirivimab/imdevimab), intravenous immunoglobulin (IVIG) for any indication, or dexamethasone specifically for treatment of COVID-19.
13. Current use of COVID-19 treatment (authorized, approved, or investigational).

14. The following exclusions related to use of an authorized or approved vaccine for SARS-CoV-2 are applicable:
    a) Receipt of any authorized or approved vaccine for SARS-CoV-2 within 48 hours prior to dosing.
    b) Planned use of any authorized or approved vaccine for SARS-CoV-2 within 90 days of study drug administration per current CDC recommendations [CDC, 2021d].
15. Receipt of any non-SARS-CoV-2 vaccines within 14 days (for non-live vaccines) or 28 days (for live vaccine) of Screening.

**Prior/Concurrent Clinical Study Experience**

16. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (e.g. casirivimab/imdevimab) or IVIG within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the Screening visit.
17. Has participated, is participating, or plans to participate during the study period in a clinical research study evaluation of any authorized, approved or investigational vaccine for SARS-CoV-2.
18. Currently enrolled in another clinical study.

**Other Exclusions**

19. Infants <24 weeks of age: maternal receipt of IVIG, SARS-CoV-2-directed convalescent plasma or SARS-CoV-2-directed mAb(s) within 3 months prior to birth or within 5 half-lives of the investigational product (whichever is longer).
20. Participants who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol through the end of the study.
21. Known hypersensitivity to any constituent present in the investigational product.

## 5.3. Lifestyle Considerations

Lifestyle considerations are not applicable to this study. Participants should be encouraged to comply with the institutional or government-recommended protocols for reducing risk of SARS-CoV-2 infection (e.g., social distancing, wearing masks).

## 5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs. Re-screening is not permitted in this study.

## 5.5. Criteria for Temporarily Delaying Enrollment

There is no reason for enrollment to be delayed in this study when inclusion/exclusion criteria are met.

# 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

An overview of the study interventions is provided in Table 5. Detailed instructions for the administration of study drug will be provided in a separate pharmacy manual.

**Table 5 Overview of Study Interventions**

| **Arm Name** | **Sotrovimab IV** | **Sotrovimab IM** |
|---|---|---|
| **Intervention Label** | Sotrovimab | Sotrovimab |
| **Type** | Biologic | Biologic |
| **Dose Formulation** | Solution in single use vial (62.5 mg/mL) | Solution in single use vial (62.5 mg/mL) |
| **Unit Dose Strength(s)** | 500 mg/vial (500 mg/8 mL) | 500 mg/vial (500 mg/8 mL) |
| **Dosage Level(s) by Weight:** | 0 to <2 years:<br>• 2 to <5 kg: 62.5 mg = 1 mL<br>• 5 to <15 kg: 125 mg = 2 mL<br>• 15 to <40 kg: 250 mg = 4 mL<br>2 to <6 years:<br>• 5 to <15 kg: 125 mg = 2 mL<br>• 15 to <40 kg: 250 mg = 4 mL<br>6 to <12 years:<br>• 15 to <40 kg: 250 mg = 4 mL<br>• ≥40 kg: 500 mg = 8 mL<br>12 to <18 years:<br>• 15 to <40 kg: 250 mg = 4 mL<br>• ≥40 kg: 500 mg = 8 mL | 0 to <2 years:<br>• 2 to <5 kg: 62.5 mg = 1 mL<br>• 5 to <15 kg: 125 mg = 2 mL<br>• 15 to <40 kg: 250 mg = 4 mL<br>2 to <6 years:<br>• 5 to <15 kg: 125 mg = 2 mL<br>• 15 to <40 kg: 250 mg = 4 mL<br>6 to <12 years:<br>• 15 to <40 kg: 250 mg = 4 mL<br>• ≥40 kg: 500 mg = 8 mL<br>12 to <18 years:<br>• 15 to <40 kg: 250 mg = 4 mL<br>• ≥40 kg: 500 mg = 8 mL |
| **Route of Administration** | IV infusion | IM injection |

| **Arm Name** | **Sotrovimab IV** | **Sotrovimab IM** |
|---|---|---|
| **Dilution with Saline** | • Participants <15 kg: none<br>• Participants ≥15 kg: 40 mL saline | None |
| **Duration of Infusion** | 30 minutes | Not applicable |
| **Use** | Experimental | Experimental |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | Sotrovimab will be provided centrally by the sponsor/designee<br>Saline will be provided by the study site. | Sotrovimab will be provided centrally by the sponsor/designee |
| **Packaging and Labeling** | Sotrovimab will be provided in a single-use vial and labeled as required per country requirement | Sotrovimab will be provided in a single-use vial and labeled as required per country requirement |
| **Current/Former Name(s) or Alias(es)** | VIR-7831, GSK4182136 | VIR-7831, GSK4182136 |

Intramuscular injection for groups receiving 1 mL, 2 mL, 4 mL or 8 mL of sotrovimab will be performed as two 0.5 mL, two 1 mL, two 2 mL, or two 4 mL injections, respectively—one in each dorsogluteal, anterolateral thigh, or deltoid muscle. Location of IM injections will be per participant/LAR preference and the clinical discretion of the investigator. All IM injections should be given at approximately the same time.

Intravenous infusion will be administered over a 30 minute period. In the adult program the length of infusions were 15 minutes, 30 minutes, and 1 hour in the COMET-PEAK, BLAZE-4, and COMET-ICE studies, respectively (COMET-PEAK included both 15 minute and 30 minute infusions). To date, 101 participants have been dosed with IV sotrovimab infused over 30 minutes in BLAZE-4 and no IRRs related to study treatment have been reported. In 159 participants that were given sotrovimab via IV infusion over 15 minutes or 30 minutes in COMET-PEAK, there were no reports of IRRs as of 23 July 2021.

Infusion time can be extended at the discretion of the Investigator or Sponsor based on infusion-related symptoms or other safety findings. Refer to Section 7.1 for procedures to follow if a participant experiences a Grade 3 or 4 IRR and Section 7.1.1 for procedures to follow if a participant experiences a Grade 2 IRR. Study intervention should be infused via a participant's central venous catheter (e.g., port, percutaneously inserted central catheter [PICC]) if he/she has one in place.

Investigational product will be administered in the clinic with staff trained in emergency care and resuscitation procedures and emergency care kit on hand during the infusion/injection and post-therapy observation periods.

Additional information about administration methods and saline dilution is provided in Section 4.3.

## 6.2. Preparation, Handling, Storage, and Accountability

Instructions for the preparation of study drug will be provided in a separate pharmacy manual.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor, and/or GSK study contact.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
7. The excipients used in the sotrovimab formulation are safe for administration in the pediatric population participating in the study.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label treatment study and participants are not randomized. All screened participants will be identified by a unique participant number that will remain consistent for the duration of the study. Upon completion of all the required Screening assessments, eligible participants will be registered into the study by the investigator or authorized site staff.

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.

## 6.4. Study Intervention Compliance

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. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5. Dose Modification

This is a single dose study and dose modifications are not applicable.

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

There will not be continued access to study intervention after the end of the study. Re-dosing with sotrovimab has not been studied; therefore, there is no evidence to support benefit of continued access to study intervention.

## 6.7. Treatment of Overdose

For this study, any dose of sotrovimab greater than the protocol-defined dose and frequency (one-time dose) will be considered an overdose. No specific treatment is recommended for an overdose. The treating physician may provide supportive measures depending on the symptoms. In the event of an overdose, the treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3. Document the quantity and/or frequency of the excess dose in the electronic case report form (eCRF).

## 6.8. Concomitant Therapy

Any vaccine or medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF, along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

While prioritizing standard clinical care, efforts should be made not to administer vaccines within 14 days (for non-live vaccines) or 28 days (for live vaccine) of dosing.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.8.1. Medication Not Permitted During the Study

Receipt of convalescent plasma from a recovered COVID-19 patient, anti-SARS-CoV-2 mAb, IVIG for any indication, or dexamethasone specifically for treatment of COVID-19 are not permitted during the study.

Receipt of any authorized or approved SARS-CoV-2 vaccine is not permitted within 90 days after dosing per CDC guidelines [CDC, 2021d].

### 6.8.2. Permitted Concomitant Medication

All medication that the participant is receiving as local, established standard of care for acute COVID-19 is permitted with the exception of those mentioned under exclusion criteria (Section 5.2).

Any concerns regarding the acceptability of potential treatments should be discussed with the medical monitor(s).

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

## 7.1. Discontinuation of Study Intervention

For IV administration, a participant will be permanently discontinued from completion of drug infusion if they experience a Grade 3 or 4 IRR (for example, life-threatening, IRRs including severe allergic or hypersensitivity reactions or severe cytokine release syndrome). Refer to Section 10.5 for management guidelines for events of anaphylaxis. Discontinuation of study intervention does not apply to IM injection.

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

### 7.1.1. Temporary Discontinuation

For IV administration, if a participant experiences a Grade 2 (moderate) IRR, investigators will be instructed to pause the infusion. The infusion may subsequently resume at a slower pace at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids).

## 7.2. Participant Discontinuation/Withdrawal from the Study

- The legal guardian and the pediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the

study staff identify any reluctance in the legal guardian or pediatric participant (e.g., signs of verbal or physical dissent) about continued participation in the study, the pediatric participant's continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

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

## 7.3. Lost to Follow Up

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

The following actions must be taken if a participant fails to complete a scheduled visit or phone call:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- If participants cannot be reached after 3 telephone calls at least 24 hours apart, their listed secondary contact person(s) or health care provider will be contacted.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

## 7.4. Liver Chemistry Increased Monitoring Criteria

Participants meeting the following liver chemistry criteria will have more frequent liver chemistry assessments performed. Refer to Section 10.9 for details.

Level 1 Monitoring

- Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) and ≥1.5x baseline value and not meeting any of the Level 2 Monitoring criteria

Level 2 Monitoring

- Both ALT ≥5xULN and ≥2x baseline value
- Both ALT ≥3xULN and ≥1.5x baseline value that persists for 4 weeks
- ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin >2xULN and at least doubled from baseline value)
- ALT ≥3xULN and International normalized ratio (INR) >1.5
- Both ALT ≥3xULN and ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

# 8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA see (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Blood samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor/designee to enable future analysis of exploratory endpoints as described in the Study Reference Manual (SRM).

- Validated and secure electronic access will be granted to Clinical Research Associates to review the participants' electronic records to verify that the information in the records matches the information entered in the Electronic Data Capture (EDC) system. If required, in the event of a Quality Assurance audit, auditor(s) may be granted access to electronic records.
- In cases where validated and secure electronic access to the participant's electronic records is not available, unredacted Source Documents (including ICF, Regulatory Documents and Source data) will be uploaded into a regulatory and data privacy-compliant cloud environment, generating certified copies of source documents (as per ICH/GCP guidelines) to be verified by the Clinical Research Associate against the information entered in the EDC. As per ICH/GCP guidelines, the PI and site staff users remain in control of the Source Documents, only site personnel can upload or invalidate source data, while only Clinical Research Associates (or auditors, as required) assigned to a given site can view the Source Documents remotely.
- The volume of blood collected should be minimized whenever possible.
- For participants ≥2 years of age
    - The total blood loss from sampling in any 24 hour period is not expected to exceed 1% of total blood volume (e.g., for a 10 kg 2 year old, 19 mL). The total blood loss from sampling during any 4-week period of time is not expected to exceed 3% of total blood volume (e.g., for a 10 kg 2 year old, 54 mL) [EMEA, 2009].
- For participants <2 years of age
    - The total blood loss from sampling on a single day is not expected to exceed 5 mL/kg of body weight (e.g., for a 2 kg neonate, 10 mL). The total blood loss from sampling during any 8-week period of time is not expected to exceed 9.5 mL/kg of body weight (e.g., for a 2 kg neonate, 19 mL) [NIH Clinical Center, 2009].

## 8.1. Efficacy

Not Applicable

## 8.2. Screening Period

Informed consent must be obtained before conducting any study procedures. Dosing will be performed within 2 days of Screening. Screening will include the assessments outlined in the SoA (Section 1.3).

The Screening visit and the Day 1 visit may occur on the same day.

### 8.2.1. Medical History

Relevant medical history within the last three years, as determined by the Investigator, should be reported. Details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing will be collected for all participants and should be

updated prior to dosing. Medical history will include baseline COVID-19 symptoms, comorbidities, and tobacco use (tobacco use will not be collected for participants <2 years of age).

### 8.2.2. SARS-CoV-2 Diagnostic Testing

Documentation of laboratory-confirmed SARS-CoV-2 infection via any validated qRT-PCR or other NAAT from any respiratory specimen collected ≤7 days prior to study entry must be confirmed for eligibility (refer to the SoA in Section 1.3) [FDA, 2021a].

Participants with a negative test prior to Screening, who are tested again at Screening and are positive for SARS-CoV-2 can be included as long as the participant has had symptoms ≤7 days from dosing.

### 8.2.3. Secondary Contact Information

In order to minimize the potential for missing data related to the safety assessments of mortality or need for hospitalization, sites should collect participant contact information for two secondary contacts (e.g., caregiver, family member, friend). The site may also request health care provider contact information and medical care facilities the participant is likely to go to if they get sick.

- Contact information for secondary contacts or health care provider will not be recorded in any eCRF. Contact information should be reviewed and updated at each home visit or outpatient clinic visit.

## 8.3. Virologic Assessments

Samples for virological analysis will be collected from participants in Cohort A and Cohort B in accordance with the laboratory manual and SoA (Section 1.3).

- Nasal mid-turbinate swabs will be collected for SARS-CoV-2 RT-PCR (validated qRT-PCR)
- Samples may also be used for resistance surveillance analysis
- On Day 1, sample collection will occur pre-dose
- CCI [redacted]
- Day 1 samples will be evaluated for SARS-CoV-2 characterization (e.g., identification of variants)

Viral load data will be summarized and compared with baseline. Details of the PD analyses will be provided in the statistical analysis plan.

CCI [redacted]

SARS-CoV-2 tests, only antibodies directed against the nucleocapsid protein will be measured on Day 29.

Participants <2 years of age will not have blood testing of anti-N or anti-S SARS-CoV-2 antibodies.

## 8.4. COVID-19 Monitoring

### 8.4.1. Monitoring of COVID-19 Signs and Symptoms

COVID-19 signs and symptoms will be reviewed at timepoints shown in the SoA (Section 1.3) to monitor COVID-19 symptom change over time.

### 8.4.2. Monitoring of COVID-19 Progression

Participants will be monitored daily from Day 1 through Day 14 and on Day 22 and Day 29 for progression of disease as shown in the SoA (Section 1.3). On days without a clinic or home visit, this monitoring will occur via a phone call. This will include questions regarding serious or life-threatening conditions such as dyspnea at rest or severe dyspnea on exertion, hemoptysis, cyanosis, or mental status changes. If a participant exhibits any of these symptoms, the site will direct the participant to seek medical attention. In addition, any healthcare encounters or new concomitant medications will be recorded.

### 8.4.3. Phone Call for Subsequent COVID-19 Illness

To monitor participants for subsequent COVID-19 illness after Day 29, participants will be called weekly from Week 5 to Week 11 and Week 13 to Week 35 (Section 1.3). This phone call will assess whether the participant was diagnosed again with COVID-19 and whether this illness resulted in any healthcare encounters. Any medications given as a result of this illness will also be recorded.

## 8.5. Safety Assessments

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

### 8.5.1. Vital Signs

- Vital signs will be recorded at visits as provided in the SoA (Section 1.3).
- Temperature (in infants, rectal preferred; otherwise, oral preferred), pulse rate, respiratory rate, blood pressure, and oxygen saturation ($SpO_2$) will be assessed.
- Day 1 vital signs will initially be monitored for 2 hours after dose administration as described in the SoA (Section 1.3). 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.

- Blood pressure and pulse measurements will be assessed in a supine or semi-supine position used consistently for that participant.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.
- An appropriately sized cuff should be used for accurate blood pressure measurement. For children in whom the appropriate cuff size is difficult to determine, the midarm circumference (measured as the midpoint between the acromion of the scapula and olecranon of the elbow, with the shoulder in a neutral position and the elbow flexed) should be obtained for an accurate determination of cuff size. The bladder length should be 80% to 100% of the circumference of the arm, and the width should be at least 40% [Flynn, 2017].

### 8.5.2. Physical Examinations

A complete (full) physical examination will be performed at Screening and on Day 1 as shown in the SoA (Section 1.3). The complete physical exam only needs to be performed once if Screening and dosing occur on the same day. A brief physical exam is required at the timepoints specified in the SoA (Section 1.3).

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

Height (or length) and weight will be measured using the appropriate method for the participant's age and plotted on age- and gender-appropriate charts so that a visual assessment can be performed relative to normative standards for height and weight and change in height and weight over time. Website links to CDC and WHO height (or length) and weight charts are provided in Section 10.7 and Section 10.8, respectively.

### 8.5.3. Electrocardiograms

A 12-lead ECG will be obtained at the timepoints described in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Triplicate ECGs will be obtained at Screening to serve as a baseline ECG for the participant; triplicate ECGs are defined as 3 individual ECGs obtained as closely as possible in succession but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minutes) recording period.

If Screening occurs on the day of dosing, only one set of triplicate ECGs will be obtained prior to dose (the additional pre-dosing ECG is not required).

Subsequent scheduled or unscheduled evaluations will be obtained as a single 12-lead ECG unless an abnormality is noted, in which case a triplicate ECG should be obtained.

Lead placement should be appropriate for the participant's age. Normal ECG values for pediatric age groups may differ from normal values in adults; therefore, normal values based on the participant's age should be used when interpreting ECGs. ECGs should be interpreted by a pediatric cardiologist.

The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding on ECGs should be reported as an AE.

Before each ECG test, the participant should be at rest for approximately 10 minutes. The participant should be in the semi-recumbent or supine position; the same position must be used for all ECG tests.

### 8.5.4. Cardiac Monitoring

Given the potential for direct myocardial involvement by SARS-CoV-2, it is possible that ADE of disease could manifest as cardiac toxicity [Huang, 2020]. To monitor this, participants who develop new or worsening cardiac symptoms, signs or ECG findings suggestive of myocarditis, acute myocardial infarction, or cardiac failure, cardiology consultation (outpatient or inpatient, depending on if the participant is hospitalized) will be recommended to guide further cardiac work up and assessment of potential cardiac events. Event details should be captured in the appropriate EDC forms.

### 8.5.5. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- Laboratory assessments for safety purposes will be performed as noted in the SoA (Section 1.3).
- Baseline for safety laboratory tests is defined as the last value obtained prior to dosing.
- Urine will be collected on Day 1 (pre-dose), Day 8, and Day 29 for analysis of albumin to creatinine ratio.
- All protocol-required laboratory tests performed, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and SoA (Section 1.3).
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study (either at any timepoint as per SoA or any unscheduled assessment) should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.

### 8.5.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- If the participant is a WOCBP (refer to Section 10.4.1 for definition), pregnancy testing (serum or high sensitivity urine as required by local regulations) should be conducted at Screening to confirm eligibility and at Week 36 or the Early Withdrawal visit.
- Additional serum or high sensitivity urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

### 8.5.7. Monitoring of Multisystem Inflammatory Syndrome in Children (MIS-C)

During the course of the study, participants will be monitored for occurrence of multisystem inflammatory syndrome in children (MIS-C). MIS-C cases will be defined as per the CDC definition [CDC, 2021e].

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

- The definitions of adverse events (AEs) or serious adverse events (SAEs) can be found in Section 10.3.
- The definitions of unsolicited and solicited AEs can be found in Section 10.3.
- AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).
- The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

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

### 8.6.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from dose administration until Week 36 at the timepoints specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from dose administration until Week 36 at the timepoints specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

### 8.6.2. Method of Detecting AEs and SAEs

- Study-site staff should instruct the legal guardians and caregivers, on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed in neonates, infants, or toddlers. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.
- Moreover, symptoms that are dependent on participant communication ability (e.g., nausea, pain, mood alterations) in younger or mentally-disabled children could potentially be at risk for under- or mis-reporting.
- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.6.3. Assessment of Severity

Standard toxicity grading according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.1 (July 2017) will be used to grade all AEs (see Section 10.3.4 and the Study Reference Manual).

### 8.6.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.6.9), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

### 8.6.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

### 8.6.6. Pregnancy

- Any pregnancies in female participants after the dose of study intervention and until 36 weeks after study drug administration will be documented.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant's pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the

neonate/child for 6 to 8 weeks after the birth, and the information will be forwarded to the sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.6.5. While the investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant after administration of study intervention should not be withdrawn from the study, unless the participant chooses to be withdrawn.
- For a female participant who becomes pregnant, this information will be shared with the study participant's legal guardian as required by local regulations.

### 8.6.7. Cardiovascular and Death Events

For any CV events detailed in Section 10.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the eCRF within 1 week of receipt of a CV event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

### 8.6.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Adverse 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, should not be reported as an AE or SAE.

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the clinical course of the disease and/or the participant's clinical status, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an AE or SAE.

For example, the following constitute events NOT meeting the AE definition:

- Hypoxemia due to COVID-19 requiring more than pre-morbid supplemental oxygen
- Hypoxemia due to COVID-19 requiring new 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).

**NOTE:** If either of the following conditions apply, then the event must be recorded and reported as an AE or SAE (instead of a disease-related event):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the natural history of the disease, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with study treatment(s).

### 8.6.9. Adverse Events of Special Interest

Adverse events of special interest are defined in the study protocol as relevant known toxicities of other therapeutic mAbs that will be monitored by the Sponsor either during or at the end of the study. Participants will be monitored for AEs and SAEs during the 2 hours post-dose (Section 1.3). 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.

Adverse events of special interests include:

- Hypersensitivity reactions (HSRs) including serious: refer to Section 2.3.1 for details and Section 10.5 for management guidance.
- Injection site reactions (ISRs): refer to Section 2.3.1 for details. Local injection site tolerability will be assessed as described in the SoA (Section 1.3). Refer to Section 8.6.3 for assessment of AE severity. and Section 10.5 for management guidance.
- Infusion related reactions (IRRs): refer to Section 2.3.1 for details and Section 7.1 and Section 7.1.1 for management guidance.
- Immunogenicity-related adverse events: refer to Section 2.3.1 for details.
- Adverse events potentially related to ADE of disease

  ADE of disease theoretically can occur via one of three previously described mechanisms:

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

  The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations [Arvin, 2020]. This study will include participant follow-up for a period of 36 weeks to assess for the potential of enhanced disease in the context

of waning sotrovimab levels, which may manifest as an increased incidence of re-infection or increased severity of re-infections after recovery from initial illness. The third mechanism is hypothesized to occur at high levels of antigen (i.e., viral load) and antibody potentially leading to immune complex deposition and complement activation in tissue sites of high viral replication. This may manifest as acute deterioration in clinical status temporally associated with sotrovimab infusion or as increased severity or duration of illness in sotrovimab-treated, COVID-19 positive participants compared to what would be clinically expected.

As described in Section 2.3.1, AEs potentially related to ADE of the disease will be reviewed by the JSRT and IDMC to assess if there is a greater than expected incidence of re-infection or disease severity (see Section 8.5.4 for cardiac monitoring).

Refer to Section 8.6.4 for requirements for follow-up assessments for all AESI.

## 8.7. Pharmacokinetics

Blood samples for serum PK will be collected as detailed in the SoA (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the sponsor or designee in the laboratory manual.

- The actual date and time (24-hour clock time) of each sample will be recorded.
- Pharmacokinetic samples will be analyzed using an appropriately validated assay method.
- Samples collected for analyses of sotrovimab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- At visits during which whole blood samples are collected to obtain serum endpoints other than PK of sotrovimab, one sample of sufficient volume can be used.
- Genetic analyses will not be performed on these whole blood or serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

A population pharmacokinetic model will be used to estimate body weight-adjusted serum clearance, volume of distribution, and (where possible) absolute IM bioavailability. Additional posterior Bayes PK parameters $C_{max}$, $T_{max}$, $AUC_{0\text{-}D5}$, $AUC_{0\text{-}D8}$, $AUC_{0\text{-}D29}$ and $AUC_{inf}$ will be calculated and summarized. A non-compartmental evaluation of $t_{1/2}$ will also be conducted.

Serum concentrations may also be combined with data from other studies evaluating sotrovimab for the purpose of population PK model performance evaluation. These analyses may include graphical plots, tabular summaries, and various linear and/or

nonlinear analyses. Details of the PK analyses will be provided in the statistical analysis plan.

## 8.8. Resistance Analysis

In order to monitor for potential resistance to sotrovimab, resistance surveillance will be conducted for all participants at baseline and at the last timepoint with virus above the limit for the sequencing assay for all participants up to Day 8 and an additional timepoint will be sequenced at Day 11 and Day 29 if still above the limit for the sequencing assay (see the SoA [Section 1.3]). Other timepoints may also be subjected to sequence analysis as needed. Deep sequence analysis of the SARS-CoV-2 spike gene may be attempted on nasal mid-turbinate samples to determine amino acid variants. For identified substitutions that qualify for phenotypic analysis, the antiviral activity of sotrovimab will be evaluated *in vitro* using a SARS-CoV-2 spike pseudovirus system.

## 8.9. Genetics

Genetics are not evaluated in this study.

## 8.10. Biomarkers

Biomarkers are not evaluated in this study.

## 8.11. Immunogenicity Assessments

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

Serum samples will be screened for antibodies binding to sotrovimab and the titer of confirmed positive samples will be reported. Samples that have positive titers will undergo assessment for neutralizing activity. Other analyses may be performed to verify the stability of antibodies to sotrovimab and/or further characterize the immunogenicity of sotrovimab.

- The detection and characterization of antibodies to sotrovimab will be performed using a validated assay method by or under the supervision of the sponsor or designee. Samples collected for detection of antibodies to study intervention may also be evaluated for sotrovimab serum concentration as described in Section 8.7 to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. At visits during which whole blood samples are collected to obtain other serum endpoints, one sample of sufficient volume can be used.

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

Samples will be collected in accordance with the laboratory manual and SoA (Section 1.3).

### 8.12. Health Economics

Health economics parameters are not evaluated in this study.

## 9. STATISTICAL CONSIDERATIONS

### 9.1. Statistical Hypotheses

There are no formal hypothesis tests associated with these objectives and no formal significance tests will be performed.

### 9.2. Analysis Sets

Separate Analysis Sets are defined for Cohorts A and B. Results will be presented by Cohort.

| Participant Analysis Set | Description |
|---|---|
| Safety (Cohort A/Cohort B) | All participants who are exposed to study intervention in Cohort A/Cohort B. |
| Pharmacokinetic (PK) (Cohort A/Cohort B) | All participants in Cohort A/Cohort B who are exposed to study intervention and who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). |
| Virology (Cohort A/Cohort B) | All participants who are exposed to study intervention in Cohort A/Cohort B and have a quantifiable SARS-CoV-2 viral load measurement at baseline. |

### 9.3. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. The analysis plan will only include planned analysis of data from this study. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

### 9.3.1. Primary Endpoint(s)

| **Primary Estimand** | |
|---|---|
| Objective | To evaluate the pharmacokinetics by IV or IM administration of sotrovimab in children from birth to <18 years |
| Variable/Endpoints | Body weight-adjusted serum clearance of sotrovimab<br>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) |
| Participant Analysis Set | Pharmacokinetic (Cohort A/Cohort B) |
| Intercurrent Event Strategy | Data analyzed as collected (treatment policy strategy) |
| Population Level Summary | PK model parameters |

| **Primary Estimand** | |
|---|---|
| Objective | To evaluate the safety and tolerability of sotrovimab by IV or IM administration |
| Variable/Endpoints | Incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESI) through Day 29 and Week 36 |
| Participant Analysis Set | Safety (Cohort A/Cohort B) |
| Intercurrent Event Strategy | Data analyzed as collected (treatment policy strategy) |
| Population Level Summary | Descriptive summary: Number and percentage of participants with ≥1 event |

### 9.3.2. Secondary Endpoints

Full details of all analysis methods for the secondary endpoints will be provided in the statistical analysis plan.

### 9.3.3. Other Safety Endpoints

Full details of all analysis methods for the other safety endpoints will be provided in the statistical analysis plan.

### 9.3.4. Exploratory Endpoints

Full details of all analysis methods for the exploratory endpoints will be provided in the statistical analysis plan.

## 9.4. Interim Analysis

Interim analysis of safety and PK data will be conducted at the following points:

- Safety data will be reviewed by the JSRT and IDMC 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.
- PK data will be reviewed and safety data will be reviewed by the JSRT and IDMC once all participants in Cohort A aged 12 to <18 years complete Day 29. Data will be reviewed to decide whether to open recruitment to participants aged 2 to <18 years in Cohort B.
- Safety data will be reviewed by the JSRT and IDMC 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.
- Safety data will be reviewed by the JSRT after half of participants are dosed in either Cohort (Cohort A or Cohort B). Data will be used to decide whether the post-dose Day 1 monitoring should be reduced to 1 hour within the same Cohort.

Further details will be added to the statistical analysis plan. The primary objectives for each cohort will be assessed once the last participant recruited in the cohort completes the Day 29 assessment. Participants will continue to complete the remaining scheduled assessments up to Week 36.

## 9.5. Sample Size Determination

Sample size evaluation 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, medium and small trials with dense, medium and sparse sampling (5 samples). 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 (medium trial, sparse sampling) was simulated 10,000 times and final precision estimated for the four reference age bands; 36 participants and no more than 5 samples per participant. 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.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
    - The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., American Academy of Pediatrics [AAP], EU Academy of Pediatrics [EAP]) or Health Department guidelines.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent and Assent Process

**Legal Guardian Consent and Pediatric Participant Assent Processes:**

- The investigator, or a person designated by the investigator, will provide the legal guardian (refer to Section 10.10: Abbreviations and Definitions) with the written ICF and the participant with the assent if applicable. They must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written assent, that meets the requirements of 21 CFR 50, local regulations, International Conference on Harmonisation (ICH) guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center after the nature of the study has been fully explained, including answering all questions regarding the study and explaining the risks and benefits, and before performance of any study-related activity.

- Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate.

- The medical record must include a statement that written informed consent from the legal guardian and assent from the pediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the clinical investigator determined that the person signing the ICF was the participant's legal guardian. The authorized person obtaining the informed consent must also sign the ICF and assent form attesting that the pediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.

- Participants and their legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.

- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.

- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.

- A copy of the informed consent and assent forms must be provided to the participant and the participant's legal guardian.

- As appropriate, participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.

- Stored samples will be coded throughout the sample storage and analysis process and will not be labelled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.

### 10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

- The participant and legal guardian must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.

- The participant and legal guardian must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The participant must be informed that information on pregnancy or contraception use may be shared with the legal guardian, subject to local regulations.

### 10.1.5. Committees Structure

An IDMC will review safety data throughout the conduct of the study at regular intervals as outlined by the IDMC charter. The roles and responsibilities of the IDMC, including membership, scope, frequency of meetings and communication plan are defined in the IDMC charter. Throughout the study, the IDMC will review safety data from all participants enrolled in either Cohort. The IDMC and JSRT will review safety data as described in Section 4.1 prior to starting subsequent stages of recruitment.

#### 10.1.5.1. Joint Safety Review Team

A JSRT comprised of team members from clinical research, global safety, and statistics from GSK and Vir, will review safety data throughout the study and will determine if a safety concern identified during instream data review needs to be escalated to the IDMC. The responsibilities of the JSRT and frequency of assessments will be outlined in the

JSRT charter. Throughout the study, the JSRT will review safety data from all participants enrolled in either Cohort.

The IDMC and JSRT will review safety data as described in Section 4.1 prior to starting subsequent stages of recruitment.

Additionally, 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.

### 10.1.6. Dissemination of Clinical Study Data

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

### 10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in data entry guidelines.

- Quality tolerance limits (QTLs) will be pre-defined in the Integrated Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent CRO document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

### 10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and

verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 10.1.9. Study and Site Start and Closure

**First Act of Recruitment**

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

**Study/Site Termination**

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

### 10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as

individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by a local laboratory at Screening for participants of all ages and at all timepoints for children <2 years. A central laboratory will be used for all timepoints besides Screening for participants ≥2 years of age.

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

**Table 6 Protocol-required Safety Laboratory Tests**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Hematocrit<br>Platelet count<br>RBC count<br>Hemoglobin | RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes | WBC count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry | BUN | Potassium | Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) | Total and direct bilirubin |
| | Creatinine | Sodium | Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)[1] | Total protein |
| | Glucose (non-fasting) | Calcium | Alkaline phosphatase[2] | Gamma-glutamyl transferase (GGT) |
| | Carbon dioxide/bicarbonate | Chloride | Lactate dehydrogenase (LDH) | Albumin |
| | Amylase | Lipase | | |
| Coagulation parameters | International Normalized Ratio (INR) time | Prothrombin time (PT) | Partial thromboplastin time (PTT) / Activated PTT (aPTT) | |
| Routine Urinalysis | • Urine albumin and urine creatinine (urine albumin-to-creatinine ratio)[3]<br>• Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if blood, protein, or leukocyte esterase is abnormal) | | | |
| Pregnancy testing | Serum/plasma or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[4] | | | |
| Other Screening Tests | All study-required Screening laboratory tests will be performed by a local laboratory | | | |

Notes:

1. Details of liver chemistry increased monitoring criteria and required actions and follow-up assessments after a liver increased monitoring event are given in Section 7.4 and Section 10.9. All events of ALT ≥3×ULN and total bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, which may indicate

severe liver injury (possible Hy's Law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase (total) is elevated, consider fractionating (e.g.: liver, bone, kidney, and intestinal isoenzymes, if available).
3. Bagged urine collection is permitted in infants and pre-continent participants for urine chemistries. Instrumentation of pediatric participants (e.g.: bladder catheterization) should be avoided wherever possible.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

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

## 10.3.1. Definition of AE

**AE Definition**

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- **Definition of Unsolicited and Solicited AE**

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

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

**Events NOT Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

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

**a. Results in death**

**b. Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

a. In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

b. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Possible Hy's Law case: ALT ≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE.
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

### 10.3.3. Definition of Cardiovascular Events

| **Cardiovascular Events (CV) Definition:** |
|---|
| Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:<br>• Myocardial infarction/unstable angina<br>• Congestive heart failure<br>• Arrhythmias<br>• Valvulopathy<br>• Pulmonary hypertension<br>• Cerebrovascular events/stroke and transient ischemic attack<br>• Peripheral arterial thromboembolism<br>• Deep venous thrombosis/pulmonary embolism<br>• Revascularization |

### 10.3.4. Recording and Follow-Up of AE and SAE

| **AE and SAE Recording** |
|---|
| • When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant AE/SAE information.<br>• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.<br>• There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.<br>• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. |
| **Assessment of Intensity** |
| Standard toxicity grading according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.1 (July 2017) will be used to grade all AEs. DAIDS Grading Table for Severity of Adult and Pediatric Adverse Events is provided in the Study Reference Manual. |

- All AEs with fatal outcome should be classified as Grade 5.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE as per Section 10.3.2, NOT when it is rated as severe.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB), in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

### 10.3.5. Reporting of SAE to GSK

**SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in Study Reference Manual (SRM).

**SAE Reporting to GSK via Paper Data Collection Tool**

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor or SAE coordinator**.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Reference Manual (SRM).

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Definitions:

**Woman of Childbearing Potential (WOCBP)**

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

1. Following menarche

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

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

For individuals with permanent infertility due to a medical cause, investigator discretion should be applied.

### 10.4.2. Contraception Guidance:

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

| |
|---|
| • oral<br>• intravaginal<br>• transdermal<br>• injectable |
| Progestogen-only hormone contraception associated with inhibition of ovulation[c]<br>• oral<br>• injectable |
| Sexual abstinence<br>• *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* |

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

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

## 10.5. Appendix 5: Management of Local Injection Site Reactions and Systemic Symptoms (Anaphylaxis)

The following information for the management of local injection site reactions and systemic symptoms is based on guidelines from the Advisory Committee on Immunization Practices (ACIP), Immunization Action Coalition (IAC), and the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network [ACIP, 2021; IAC, 2019; Sampson, 2006].

### A. Local Injection Site Reactions

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

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

### B. Systemic Reactions/Anaphylaxis

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

**Diagnosis of Anaphylaxis**

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

**Danger Signs include:**

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

- Chest pain
- Collapse

**Management of Anaphylaxis**

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

1. Call for additional medical assistance; activate emergency medical services.
2. Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry.
3. First-line treatment [Sicherer, 2017;Hegenbarth, 2008; IAC, 2019]:
    - Administer epinephrine (1.0 mg/mL) aqueous solution (1:1000 dilution) – 0.01 mg/kg (maximum 0.3 mg [0.3 mL] in a prepubertal child, maximum 0.5 mg [0.5 mL] in a teenager) IM in the anterolateral thigh. May be repeated every 5 to 15 minutes up to 3 times.
    - If using an epinephrine auto-injector (round weight to nearest kg):
        - infant 7.5 to 14 kg (approximately 16.5 to 30 lbs): 0.1 mg autoinjector IM in the anterolateral thigh. (If 0.1 mg autoinjector is unavailable, use a 0.15 mg autoinjector)
        - child 15 to 29 kg (approximately 33 to 64 lbs): 0.15 mg autoinjector IM in the anterolateral thigh
        - child or teenager ≥30 kg (approximately greater than 66 lbs): 0.3 mg autoinjector IM in the anterolateral thigh
        - May be repeated every 5 to 15 minutes up to 3 times.
4. Optional treatment (antihistamine) [IAC, 2019]:

    Diphenhydramine 1-2 mg/kg/dose oral/IV/IM (40 mg maximum single dose for patients <12 years; 100 mg maximum single dose for patients ≥12 years)
    OR
    Hydroxyzine 0.5-1 mg/kg/dose oral/IM (maximum 100 mg single dose).
5. Give oxygen (8-10 L/minute) via facemask, as needed.
6. Normal saline rapid bolus – treat hypotension with rapid infusion of 20 mL/kg IV. Re-evaluate and repeat fluid boluses (20 mL/kg), as needed.
7. Monitor patient until emergency medical services arrive.

## 10.6. Appendix 6: Medical Diagnoses with Regards to Participants at High Risk of Disease Progression

Cardiovascular Disease: congenital heart disease, hypertension, cardiomyopathy, heart failure

Genetic or Metabolic Diseases: Pompe Disease, Mucopolysaccharidoses, glycogen storage diseases, fatty acid oxidation disorders, maple syrup urine disease, organic acidemias

Pulmonary Disease: moderate to severe asthma, chronic lung disease, obstructive sleep apnea, Cystic Fibrosis

Neurologic Disease: seizure disorder, global developmental delay, cerebral palsy, or structural brain defect/malformation

Immunosuppressed: primary immunodeficiency (e.g., Severe Combined Immunodeficiency), HIV infection with CD4+ count <200 cells/$mm^3$, solid organ or bone marrow transplant, long-term use of systemic corticosteroids (defined by either ≥0.5 mg/kg/day by body weight or ≥20 mg/day prednisone equivalents [whichever is the lower dose of the two] taken for ≥2 weeks, immunosuppressive biologic agents (e.g., rituximab), and disease-modifying anti-rheumatic drugs (e.g., azathioprine, methotrexate, leflunomide).

## 10.7. Appendix 7: CDC Weight and BMI Growth Charts

Refer to the following CDC length-for-age; weight-for-age percentiles or BMI charts:

- **Boys birth to 36 months:** Birth to 36 months: Boys length-for-age and weight-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Published May 30, 2000 and modified April 20, 2001. https://www.cdc.gov/growthcharts/data/set1clinical/cj41l017.pdf. Accessed July 26, 2021.
- **Girls birth to 36 months:** Birth to 36 months: Girls length-for-age and weight-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Published May 30, 2000 and modified April 20, 2001. https://www.cdc.gov/growthcharts/data/set1clinical/cj41l018.pdf. Accessed July 26, 2021
- **Boys 2 to >18 years:** 2 to 20 years: Boys body mass index-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Published May 30, 2000 and modified October 16, 2000. https://www.cdc.gov/growthcharts/data/set1clinical/cj41l023.pdf. Accessed July 26, 2020.
- **Girls 2 to >18 years:** 2 to 20 years: Girls body mass index-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Published May 30, 2000 and modified October 16, 2000. https://www.cdc.gov/growthcharts/data/set1clinical/cj41l024.pdf. Accessed July 26, 2021.

## 10.8. Appendix 8: World Health Organization (WHO) Weight-For-Age Curves

Refer to the following WHO weight-for-age percentiles:

- **Boys birth to 6 months:** World Health Organization (WHO). WHO Child Growth Standards. Weight-for-age: Boys. https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-age/boys-charts---weight-for-age-birth-to-6-months-(percentiles).pdf?sfvrsn=2a49ab55_6. Accessed July 26, 2021.
- **Girls birth to 6 months:** World Health Organization (WHO). WHO Child Growth Standards. Weight-for-age: Girls. https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-age/girls-charts---weight-for-age-birth-to-6-months-(percentiles).pdf?sfvrsn=52e7206c_6. Accessed July 26, 2021.
- **Boys: 2 to 5 years:** World Health Organization (WHO). WHO Child Growth Standards. BMI-for-age Boys. https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/body-mass-index-for-age/boys-chart--length-for-age-2-to-5-years-(percentiles).pdf?sfvrsn=e2a33b7a_0. Accessed July 26, 2021.
- **Girls 2 to 5 years:** World Health Organization (WHO). WHO Child Growth Standards. BMI-for-age Girls. https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/body-mass-index-for-age/girls-table--length-for-age-2-to-5-years-(percentiles).pdf?sfvrsn=b7ccd64e_2. Accessed July 26, 2021.

# 10.9. Appendix 9: Liver Event Increased Monitoring Criteria

## 10.9.1. Level 1 Monitoring

In the event that the participant develops elevations in liver enzyme parameters as defined below, an increase to liver chemistry monitoring (i.e., at weekly intervals), will apply.

| **Liver Chemistry Increased Monitoring Criteria - Level 1 Liver Monitoring** | |
|---|---|
| **Criteria** | **Actions** |
| ALT ≥3x ULN and ≥1.5x baseline value and not meeting any Level 2 monitoring criteria**,** **without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks | • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety.<br>• Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they stabilize or return to within baseline or normal limits<br>• If, during monitoring, ALT increases to ≥5xULN and ≥2x baseline value or remains ≥3x ULN and ≥1.5x baseline value for ≥4 weeks, or if total bilirubin increases to ≥2xULN, refer to Level 2 monitoring guidance below.<br>• If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until they stabilize or return to within baseline or normal limits. Alternatively, the monitoring can return to standard as per protocol (if applicable) or stopped when the investigator and medical monitor agree that values are stable or no longer significantly abnormal (this may require local investigation of potential causes for liver chemistry abnormality) |

## 10.9.2. Level 2 Monitoring

In the event that the participant develops elevations in liver enzyme parameters as defined below, an increase to liver chemistry monitoring at more frequent intervals (i.e., twice weekly), will apply.

| **Liver Chemistry Monitoring Criteria - Level 2 Liver Monitoring** | |
|---|---|
| **ALT absolute** | **Both** ALT ≥5xULN **and** ≥2x baseline value |
| **ALT Increase** | **Both** ALT ≥3xULN **and** ≥1.5x baseline value that persists for 4 weeks |

| **Liver Chemistry Monitoring Criteria - Level 2 Liver Monitoring** | |
|---|---|
| **Bilirubin[1, 2]** | ALT ≥3xULN **and** total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin >2xULN and at least doubled from baseline value) |
| **INR[2]** | ALT ≥3xULN **and** INR>1.5 |
| **Symptomatic[3]** | **Both** ALT ≥3xULN **and** ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity |

| **Required Actions, Monitoring and Follow up Assessments** | |
|---|---|
| **Actions** | **Follow Up Assessments** |
| • Report the event to GSK within 24 hours<br>• Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2]<br>• Perform liver event follow up assessments as described in the Follow up Assessment column<br>• Monitor the participant until liver chemistries stabilize or return to within baseline or normal limits (see **MONITORING**)<br>**MONITORING:**<br>**If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24 hours**<br>• Monitor participants twice weekly until liver chemistries stabilize or return to within baseline or normal limits<br>• A specialist or hepatology consultation is recommended<br>**For All other criteria (total bilirubin <2xULN and INR ≤1.5):** | • Viral hepatitis serology[4]<br>• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend<br>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.<br>• Fractionate bilirubin, if total bilirubin[1] ≥2xULN<br>• Obtain complete blood count with differential to assess eosinophilia<br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form<br>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications<br>• Record alcohol use on the liver event alcohol intake form<br>**If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:**<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and |

| **Liver Chemistry Monitoring Criteria - Level 2 Liver Monitoring** | |
|---|---|
| • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours**<br>• Monitor participants weekly until liver chemistries stabilize or return to within baseline or normal limits | quantitative total immunoglobulin G (IgG or gamma globulins)<br>• Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury<br>• Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging forms<br>• Liver biopsy may be considered and discussed with local specialist if available, for instance:<br>○ In patients when serology raises the possibility of autoimmune hepatitis (AIH)<br>○ In patients when suspected drug induced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention<br>○ In patients with acute or chronic atypical presentation:<br>• If liver biopsy conducted complete liver biopsy form. |

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin >2xULN and at least doubled from baseline value) or ALT ≥3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or RNA PCR test.

## 10.10. Appendix 10: Abbreviations and Trademarks

| Term | Definition |
|---|---|
| µg | Micrograms |
| λz | Apparent terminal elimination rate constant |
| $\%AUC_{exp}$ | Area under the plasma concentration-time curve extrapolated from time to infinity as a percentage of total AUC |
| %CV | Percent coefficient of variation |
| AAP | American Academy of Pediatrics |
| ACE | angiotensin converting enzyme |
| ACIP | Advisory Committee on Immunization Practices |
| ADA | Anti-drug antibodies |
| ADE | Antibody dependent enhancement |
| AE(s) | Adverse event(s) |
| AESI | Adverse events of special interest |
| AIH | autoimmune hepatitis |
| ALT | Alanine aminotransferase |
| Anti-N | Anti-nucleocapsid |
| Anti-S | Anti-spike |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{0-DX}$ | Area under the serum concentration-time curve from time zero to study Day X |
| $AUC_{DX-Y}$ | Area under the serum concentration-time curve, from Day X to Day Y |
| $AUC_{inf}$ | Area under the serum concentration-time curve from time zero to infinity |
| $AUC_{last}$ | Area under the serum concentration-time curve from time zero to time of last measurable concentration |
| BiPAP | Bilevel positive airway pressure |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| $C_{last}$ | Last measurable serum concentration |
| $C_{max}$ | Maximum observed concentration |
| CA | Competent Authority |

| Term | Definition |
|---|---|
| Caregiver | Delegated primary caregiver(s) who will be responsible for ensuring the study activities are conducted per protocol, e.g., accompany the participant to the study site on each assessment day according to the Schedule of Activities (SoA); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed; help the study-site personnel ensure follow-up. This person may be the legal guardian, or another appropriate person, delegated by the legal guardian. |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CL | Clearance |
| CLIA | Clinical Laboratory Improvement Amendments |
| CONSORT | Consolidated Standards of Reporting Trials |
| CoV | Coronavirus |
| COVID-19 | Coronavirus disease 2019 |
| CPAP | Continuous positive airway pressure |
| CPK | Creatine phosphokinase |
| CRF | Case report form |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| CTFG | Clinical Trial Facilitation Group |
| CV | Cardiovascular |
| d | Day(s) |
| DAIDS | Division of acquired immune-deficiency syndrome |
| DCO | Data cut off |
| DILI | Drug induced liver injury |
| DOL | Day of life |
| DSMB | Data and Safety Monitoring Board |
| EAP | EU Academy of Pediatrics |
| EC | Ethics committee |
| $EC_{50}$ | Half maximal effective concentration |
| $EC_{90}$ | 90% effective concentration |

| Term | Definition |
|---|---|
| ECG(s) | Electrocardiogram(s) |
| ECMO | Extracorporeal membrane oxygenation |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EEA | European economic area |
| EGA | Estimated gestational age |
| EOS | End of study |
| ESR | Erythrocyte sedimentation rate |
| EU | European Union |
| EUA | Emergency use authorization |
| EW | Early withdrawal |
| F | Bioavailability |
| FcγR | Fc Gamma Receptor |
| FDA | Food and Drug Administration |
| FI | Formalin-inactivated |
| FIH | First-in-human |
| GCP | Good clinical practice |
| Gen1 | Generation1 |
| Gen2 | Generation2 |
| GGT | Gamma-glutamyl transferase |
| GLDH | Glutamate dehydrogenase |
| GSK | GlaxoSmithKline |
| HCG | Human chorionic gonadotropin |
| HHS | Health and Human Services |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HSRs | Hypersensitivity reactions |
| IB | Investigator's brochure |
| IAC | Immunization Action Coalition |
| $IC_{90}$ | 90% inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use |
| ICU | Intensive care unit |

| Term | Definition |
|---|---|
| IDMC | Independent data monitoring committee |
| IEC(s) | Independent ethics committee(s) |
| IgG | Immunoglobulin G |
| IgG1 | Immunoglobulin G1 |
| IL-6 | Interleukin 6 |
| IM | Intramuscular |
| INR | International normalized ratio |
| IQ | Inhibitory quotient |
| IRB(s) | Institutional review board(s) |
| IRR | Infusion related reaction |
| IRRs | Infusion related reactions |
| IRT | Interactive Response Technology |
| ISR | Injection site reaction |
| iSRC | Internal Safety Review Committee |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| IV | Intravenous |
| IVIG | Intravenous immunoglobulin |
| JSRT | Joint safety review team |
| kg | kilograms |
| $kg/m^2$ | Kilograms per meter square |
| L | Liter |
| LAM | Lactational amenorrhea method |
| lbs | Pounds |
| LDH | Lactate dehydrogenase |
| LLQ | Lower limit of quantification |
| LS | Fc modification |
| LAR | Legally authorized representative |
| Legal guardian | Parent(s) (preferably both if available or as per local requirements), legally appointed guardian(s), or legally acceptable representative(s), as defined by national and local laws and regulations, who consent(s) on behalf of the minor. For the purposes of this study, all references to informed consent and assent refer to the pediatric participant (child) and his or her legal guardian who have provided consent (and assent as applicable) according to the Informed Consent Process and Assent Form |

| Term | Definition |
|---|---|
| | described in Section 10.1.3 Informed Consent and Assent Process. |
| mAb | Monoclonal antibody |
| MARM | Monoclonal antibody-resistant mutant |
| MCH | Mean corpuscular volume |
| MCV | Mean corpuscular hemoglobin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| MIS-A | Multisystem inflammatory syndrome in adults |
| MIS-C | Multisystem inflammatory syndrome in children |
| min | Minute |
| mL | Milliliter |
| $mm^3$ | Cubic milliliter |
| Mm Hg | Millimeters of mercury |
| MSDS | Material safety data sheet |
| NAAT | nucleic acid amplification test |
| NHANES | National Health and Nutrition Examination Survey |
| NIH | National Institute of Health |
| NQ | Non-quantifiable |
| PCR | Polymerase chain reaction |
| PD | Pharmacodynamics |
| Pediatric participant | Minor child participating in research study |
| PI | Principal investigator |
| PICC | Percutaneously inserted central catheter |
| PK | Pharmacokinetic(s) |
| PT | Prothrombin time |
| qRT-PCR | Quantitative reverse transcriptase polymerase chain reaction |
| QTLs | Quality tolerance limits |
| RBC | Red blood cell |
| RBD | Receptor binding domain |
| RBM | receptor-binding motif |
| RNA | Ribonucleic acid |
| RSE | Relative standard error |
| RSV | Respiratory syncytial virus |

| Term | Definition |
|---|---|
| RT-PCR | Reverse transcriptase polymerase chain reaction |
| SA | South Africa |
| SAE(s) | Serious adverse event(s) |
| SARS | Severe acute respiratory syndrome |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus-2 |
| SD | Standard deviation |
| SGOT | Serum glutamic-oxaloacetic transaminase |
| SGPT | Serum glutamic-pyruvic transaminase |
| SoA | Schedule of activities |
| SoC | Standard of care |
| SRM | Study reference manual |
| SRT | Safety review team |
| SUSARs | Suspected unexpected serious adverse reactions |
| $t_{1/2}$ | Terminal elimination half-life |
| $T_{last}$ | Time of the last quantifiable concentration |
| $T_{max}$ | Time to reach $C_{max}$ |
| ULN | Upper limit of normal |
| UK | United Kingdom |
| US | United States of America |
| V | Variance |
| $V_{ss}$ | Volume of distribution at steady state |
| $V_z$ | Apparent volume of distribution during terminal phase |
| Vir | Vir Biotechnology, Inc. |
| WBC | White blood cell |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| WT | Wild type |
| Yr | Years |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| None |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| MedDRA |

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