SAFETY SUBSTUDY CLINICAL STUDY PROTOCOL

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

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

Compound Number or Name: VIR-7831 (sotrovimab; GSK4182136)

Protocol Version & Date: Amendment #4, 27 MAY 2022

Brief Substudy Title: Intravenous single ascending dose VIR-7831 (sotrovimab) for mild/moderate COVID-19

Study Phase: Phase 3

Acronym: COMET-TAIL (**CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial– **T**reatment of **A**cute COVID-19 with **I**ntramuscular monoc**L**onal antibody)

Sponsor Name and Legal Registered Address:

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

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Regulatory Agency Identifying Number(s):

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INVESTIGATOR SIGNATURE PAGE

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STUDY ACKNOWLEDGMENT

Title:

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

This protocol has been approved by Vir Biotechnology, Inc. The following signature documents this approval.

PPD , MD Vir PPD	*{See Appended Electronic Signature Page}*
Printed Name	**Signature and Date**

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vir Biotechnology, Inc. I will discuss this material with them to ensure they are fully informed about the drugs and the study.

Principal Investigator Printed Name	**Signature**
	Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Rationale:

There is an urgent medical need for therapeutics for the treatment of Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) infection, the cause of coronavirus disease 2019 (COVID-19). Early treatment of mild and moderate disease in participants could prevent the more severe sequelae of COVID-19 requiring hospitalization, such as respiratory failure, thromboembolic disease leading to pulmonary embolism and stroke, arrhythmias, and shock. Furthermore, a potent treatment given early in disease could ameliorate the severity and duration of COVID-19 and potentially reduce transmission.

Vir Biotechnology, Inc. (Vir) has developed a fully human neutralizing anti-SARS-CoV-2 antibody (Pinto 2020), sotrovimab (also known as VIR-7831; GSK4182136), which has an Fc -modification ("LS") that is designed to increase half-life (Ko 2014). Sotrovimab, administered intravenously, has been evaluated in a Phase 3 randomized, multi-center study to assess the safety and efficacy for the early treatment of COVID-19 in non-hospitalized participants (VIR-7831-5001; GSK study 214367; COMET-ICE). The COMET-ICE study used the first-generation formulation of sotrovimab (Gen1) which could only be given intravenously. On 10 Mar 2021, the independent data monitoring committee of COMET-ICE recommended that the study be stopped for enrollment due to evidence of clinical efficacy. This was based on an interim analysis of data from 583 participants which demonstrated an 85% (p=0.002) reduction in hospitalization or death in participants receiving sotrovimab compared to placebo (Vir 2021).

The COMET-TAIL study was then designed to assess the efficacy, safety, and tolerability of intramuscular (IM) sotrovimab versus intravenous (IV) sotrovimab when given to high-risk participants for the treatment of mild/moderate COVID-19. This study evaluated the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab in preventing progression of COVID-19 by utilizing a non-inferiority (NI) design. Enrollment was completed on 19-AUG-2021 and the day 29 analysis indicated the following: in the IM administration (500mg) arm of the trial, there was a 2.7% rate of progression to hospitalization for more than 24 hours or death through Day 29 of the trial, compared to 1.3% in the IV administration arm (also 500 mg). The adjusted difference between the IM and IV arms of the trial was 1.11% with a 95% confidence interval (CI) of -1.24% to 3.45%. The upper bound of the 95% CI was within the predetermined 3.5% non-inferiority margin set for the trial's primary endpoint in consultation with the US Food and Drug Administration (FDA).

Since then, several factors have contributed to the need for evaluation of different doses of sotrovimab. First, the development of the Omicron variant and its sublineages has caused the landscape to evolve substantially as described in the COVID-19 treatment guidelines from the NIH (COVID-19 Treatment Guidelines Panel 2022). Understanding the safety and tolerability of sotrovimab across a broader dose range will provide the data should a higher dose of sotrovimab be required to treat a variant that is less susceptible to sotrovimab in the future. Additionally, evaluation of sotrovimab across a range of doses will allow for additional clinical pharmacology evaluation of population PK parameters.

Thus, this study will now consist of two parts, the original protocol and the safety substudy. In the safety substudy, the aim will be to evaluate the safety and tolerability of a single ascending dose of sotrovimab when given for the treatment of mild/moderate COVID-19 to participants at high risk of disease progression. It will also evaluate the safety and tolerability of different infusion times. The existing non-clinical and clinical safety data support the evaluation of sotrovimab across the range of doses in this substudy.

Objectives and Endpoints (Safety Substudy):

Objectives	Endpoints
Primary	
Safety Describe the safety and tolerability up through Day 8 of high dose ascending intravenous sotrovimab	• Occurrence of adverse events (AEs) through Day 8 • Occurrence of serious adverse events (SAEs) through Day 8 • Occurrence of adverse events of special interest (AESIs) through Day 8 • Occurrence of disease related events (DREs) through Day 8
Secondary	
Safety Describe the safety and tolerability up through Week 36 of high dose ascending intravenous sotrovimab	• Occurrence of adverse events (AEs) through Week 12 • Occurrence of serious adverse events (SAEs) through Week 36 (end of study) • Occurrence of adverse events of special interest (AESIs) through Week 12 • Occurrence of disease related events (DREs) through Week 12
Safety Assess the immunogenicity up through Week 24 of high dose ascending intravenous sotrovimab	Incidence and titers (if applicable) of serum anti-drug antibody (ADA) and neutralizing antibody (if applicable) to sotrovimab through Week 24
Pharmacokinetics Assess the pharmacokinetics (PK) up to Week 24 of high dose ascending sotrovimab in serum following IV administration	IV sotrovimab pharmacokinetics (PK) in serum through Week 24
Exploratory	
Efficacy Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Hospitalization > 24 hours for acute management of illness due to any cause OR • Death
Efficacy Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR

Objectives	Endpoints
	• Hospitalization for acute management of illness for any duration and for any cause OR • Death
Efficacy Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of COVID-19 respiratory disease	Development of severe and/or critical respiratory COVID-19 as manifested by requirement for respiratory support (including oxygen) at Day 8, Day 15, Day 22, and Day 29
Efficacy Describe the effect of high dose ascending intravenous sotrovimab on the incidence of ICU stay and mechanical ventilation use through Day 29	Incidence of participants requiring ICU stay or mechanical ventilation through Day 29
Resistant Mutants Monitor SARS-CoV-2 resistant mutants against sotrovimab through Day 29	• SARS-CoV-2 resistance mutants to sotrovimab at baseline • Emergence of viral resistance mutants to mAb by SARS-CoV-2
Virologic Activity Evaluate the virologic activity of high dose ascending intravenous sotrovimab in reducing SARS-CoV-2 viral load through Day 29	• Change from baseline in viral load in nasal secretions by qRT-PCR during the follow-up period at Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29 • Undetectable SARS-CoV-2 in nasal secretions by qRT-PCR at Day 3, Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29 • Proportion of participants with a persistently high SARS-CoV-2 viral load at Day 8 by qRT-PCR

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Overall Design:

The safety substudy is designed as a multi-center, open label substudy of high dose intravenous sotrovimab in participants with early, mild/moderate COVID-19 who are not on supplemental oxygen and are at risk for disease progression. Participants will receive an IV infusion of sotrovimab at different doses and infusion times (2000 mg infused over 60 minutes [planned], 30 minutes [optional] and 15 minutes [optional]) and up to 3000 mg (infused over 90 minutes [optional]) depending on which cohort the participant is enrolled in.

A total of up to 500 participants will be enrolled in this substudy and the cohorts will occur as outlined in the study schema (Section 1.2).

- Cohort A: Approximately 200 participants will be enrolled in Cohort A and receive 2000 mg of sotrovimab infused over 60 minutes.
    - 30 participants will be enrolled in a safety lead in, and relevant safety data through Day 8 will be reviewed by the Joint Safety Review Team (JSRT). Note, there will be no pause in Cohort A while the safety lead in data is reviewed.
    - 170 additional participants will then be enrolled to complete Cohort A. Enrollment will pause and a review of relevant safety data through Day 8 for these remaining participants in Cohort A will be performed by the JSRT. Looking at the totality of the data for 200 participants, the JSRT will make a safety assessment and a decision to open Cohorts B1 and/or C will be made.
- Optional Cohort B1: If a decision to proceed to cohort B1 is made, approximately 50 participants will receive 2000 mg of sotrovimab infused over 30 minutes. The JSRT will then pause and review the relevant safety data through Day 8 from Cohort B1. Following the JSRT's safety assessment, a decision to open Cohort B2 will be made.
- Optional Cohort B2: If a decision to proceed to Cohort B2 is made, approximately 50 participants will be enrolled, and they will each receive 2000 mg of sotrovimab infused over 15 minutes. Review of relevant safety data through Day 8 will then be performed by the JSRT.
- Optional Cohort C: If a decision to proceed to Cohort C is made, approximately 200 participants will be enrolled in Cohort C, and they will each receive up to 3000 mg of sotrovimab, infused over 90 minutes. Note that this cohort may occur immediately after Cohort A.
    - 30 participants will be enrolled in a safety lead in, and relevant safety data through Day 8 will be reviewed by the JSRT. Note, there will be a pause in enrollment while relevant safety data through day 8 from the safety lead in group is reviewed.
    - 170 additional participants will then be enrolled into this cohort. The JSRT will then meet to review safety data through Day 8 from this complete cohort.
    - If a lower dose than 2000 mg is selected for this cohort, there will be no safety lead-in for Cohort C and the infusion and monitoring times will be determined following safety review by the JSRT based on available safety data.

Cohorts B1, B2 and C will all be considered optional cohorts and can be opened following completion of the Cohort A safety assessment by the JSRT (B1 and C; B2 following JSRT safety assessment of B1).

After IV infusion, participants in the safety lead in Cohort A, and potentially Cohort C if a dose higher than 2000 mg is administered, will be monitored for 2 hours with vital signs assessments performed at 15 minutes, 30 minutes, 45 minutes, 1 hour and 2 hours. Participants in the remainder of Cohort A (and potentially Cohort C), Cohorts B1 and B2 will be monitored for up to 1 hour. As detailed in the Schedule of Activities, participants will be actively monitored on an outpatient basis with frequent collection of safety information through weekly in-clinic evaluations at Weeks 1, 2, 3, and 4, nasopharyngeal swabs for virology, and blood draws for PK sampling. Starting at Week 8, participants will be monitored monthly via phone call or in-clinic evaluation to assess for the incidence and severity of subsequent COVID-19 illness, if any, for a total of 36 weeks from dosing.

Number of Participants:

Approximately 200 participants (up to 500 with the optional cohorts) will be enrolled into this safety substudy.

In Cohort A of the safety substudy, 200 participants will be enrolled to receive a single 2000 mg IV infusion of sotrovimab over 60 minutes. Optional Cohorts B1 and B2 (in which participants will receive 2000 mg IV infusion of sotrovimab over 30 minutes and 15 minutes, respectively) will each enroll 50 participants.

Optional Cohort C (in which participants will receive up to 3000 mg IV infusion of sotrovimab over 90 minutes) will enroll 200 participants.

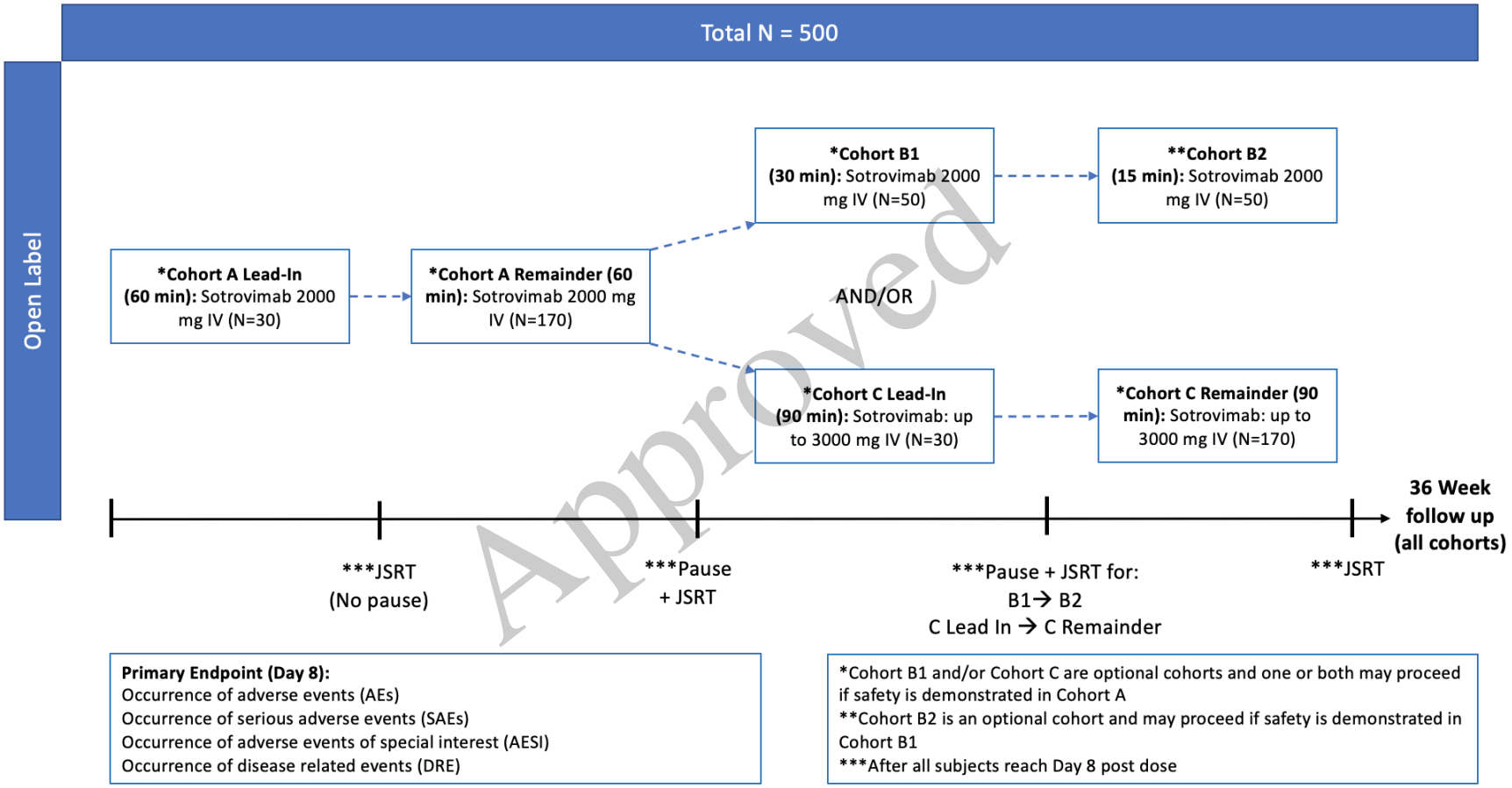
Intervention Groups and Duration:

Screening assessments in the safety substudy will be performed within 48 hours prior to randomization. There is no required minimum amount of time from screening to randomization provided that all eligibility criteria are met/confirmed.

Eligible participants will be treated with a single IV dose of 2000 or up to 3000 mg sotrovimab on Day 1 (depending on which cohort the participant is in) and followed for up to 36 weeks.

This is an open label study and all participants enrolled will receive sotrovimab treatment. Should multiple *optional* cohorts (i.e., Cohort B1 and Cohort C) be enrolling at the same time, participants will be randomly assigned to a cohort using a pre-defined schema.

1.2. Study Schema



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1.3. Schedule of Activities

Study Stage	**Screening**	**Dosing**	**Follow-up Period**														
Study Visit Week			**W1**			**W2**		**W3**	**W4**	**W8** [i]	**W12**	**W16** [i]	**W20**	**W24 (EW**[j]**)**	**W28** [i]	**W32** [i]	**W36** [i] **(EOS/EW)**
Study Visit Day ± Visit Window	**D -2 to 1**	**D1**	**D 3**	**D5± 1**	**D8± 1**	**D11± 1**	**D15± 1**	**D22± 1**	**D29±2**	**D57± 4**	**D85± 7**	**D113± 7**	**D141± 7**	**D169± 7**	**D197±7**	**D224± 7**	**D252±7**
Informed consent	X																
Demography	X																
Medical history	X																
Inclusion/exclusion criteria including baseline COVID-19 symptoms	X																
Physical examination[a]	X[a]	X[a]	X[a]		X[a]		X[a]	X[a]	X[a]								
Body weight & height	X																
Vital signs (including O2 saturation)	X	X[b]			X		X	X	X					X			
Local safety lab assessments	X[c]																
Laboratory assessments		X[d]			X		X		X								
SARS-CoV-2 diagnostic test [h] (point-of-care or local laboratory test)	X[h]																
Pregnancy test	X													X			
Electrocardiogram	X[e]																
Enrollment		X															
Randomization[l]		X															
Study drug administration[k]		X															
Nasopharyngeal swab for virology		X[d]	X	X	X	X	X	X	X								
Blood sample for PK analysis		X[f]	X	X	X		X		X		X		X	X			
Blood sample for anti-drug antibody		X[d]							X		X		X	X			
Phone call for subsequent COVID19 illness[m]										X		X			X	X	X
Clinic visit for subsequent COVID19 illness[m]											X		X	X			
Review/record AE/SAE		X[g]															
Concomitant medications		X															

[a] Complete physical examination should be performed on Day 1; all other visits should be symptom-directed physical examinations.
[b] For lead-ins in Cohorts A and C, vital signs on Day 1 should be recorded prior to dose administration and at 15 mins (± 5 mins) and 30 mins (± 5 mins), 45 min (± 5 min), 1 hour (± 5 mins), and 2 hours (± 5 mins) post dosing. For all other participants (outside of those included in the lead-ins in Cohorts A and C), vital signs should be recorded at 15 mins (± 5 mins), 30 mins (± 5 mins), 45 min (± 5 min) and 1 hour (± 5 mins) post dosing
[c] All local lab assessments may be performed or not as determined necessary by the investigator or required by local regulations.
[d] On Day 1, sample collection will occur pre-dose.
[e] Electrocardiogram at screening only for participants with a history of cardiovascular disease or diabetes
[f] On Day 1, PK sample will be collected pre-dose and at the end of infusion
[g] Adverse events will be assessed up to Week 12 post dose. Serious adverse events (SAEs) will be assessed up to Week 36.

[h] Participants may be tested at screening if symptom onset ≤ 7 days, but dosing (D1 visit) must also occur ≤ 7 days of symptom onset.
[i] Week 8, Week 16, Week 28, Week 32 and Week 36 are planned as site phone calls to participants only.
[j] If subject withdraws early from the study prior to Week 24, then the W24 visit assessments will be performed as the EW visit. If subject withdraws early from the study after Week 24, the W36 visit assessments will be performed as the EW visit.
[k] Cohort A 2000 mg to be infused over 60 minutes, Cohort B1 2000 mg to be infused over 30 minutes, Cohort B2 2000 mg to be infused over 15 minutes, Cohort C (up to 3000 mg to be infused over 90 minutes if 3000 mg is selected)
[l] Note, randomization may only apply if enrolling Cohorts B1 (2000 mg IV over 30 minutes) and Cohort C (up to 3000 mg IV over 90 minutes if 3000 mg is selected) simultaneously
[m] Clinic visits should be planned only when study samples need to be collected

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2. INTRODUCTION

2.1. Study Rationale

In this amendment, the safety substudy is designed as a phase 3, multi-center, open label study of intravenous (IV) administration of sotrovimab, a monoclonal antibody (mAb) against SARS-CoV-2 for the prevention of progression of mild/moderate COVID-19 in participants 18 years old and older at high risk of disease progression. High-risk adults include participants ≥55 years old regardless of co-morbidities and individuals age 18 or older with comorbidities associated with worse outcomes in adults, including diabetes, obesity (BMI≥30), chronic kidney disease, congestive heart failure, chronic lung diseases (i.e. chronic obstructive pulmonary disease, moderate to severe asthma requiring steroids, interstitial lung disease, cystic fibrosis, and pulmonary hypertension), immunosuppressive disease or immunosuppressive medications, or chronic liver disease (CDC 2021). The study will include participants infected with SARS-CoV-2, the virus that causes COVID-19, as confirmed by local laboratory tests and/or point of care tests.

Enrollment in the study will be performed at study site, based on hospital local practice. If a patient agrees to participate and qualifies, his/her primary doctor will be informed as per local regulation of his/her study participation by the study doctor.

Sotrovimab has been studied in a Phase 3 placebo-controlled trial evaluating the efficacy of sotrovimab in preventing progression of COVID-19 in high-risk participants with mild/moderate COVID-19 (VIR-7831-50001; COMET-ICE). On 10 Mar 2021, the independent data monitoring committee for COMET-ICE recommended that the study be stopped for enrollment due to evidence of clinical efficacy. This was based on an interim analysis of data from 583 participants which demonstrated an 85% (p=0.002) reduction in hospitalization or death in participants receiving sotrovimab compared to placebo. Sotrovimab was well-tolerated with no safety signals detected. (Vir 2021)

The COMET-TAIL study was then designed to assess the efficacy, safety, and tolerability of intramuscular (IM) sotrovimab versus intravenous (IV) sotrovimab when given to high-risk participants for the treatment of mild/moderate COVID-19. This study evaluated the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab in preventing progression of COVID-19 by utilizing a non-inferiority (NI) design. Enrollment was completed on 19-AUG-2021 and the day 29 analysis indicated the following: in the IM administration (500mg) arm of the trial, there was a 2.7% rate of progression to hospitalization for more than 24 hours or death through Day 29 of the trial, compared to 1.3% in the IV administration arm (also 500 mg). The adjusted difference between the IM and IV arms of the trial was 1.11% with a 95% confidence interval (CI) of -1.24% to 3.45%. The upper bound of the 95% CI was within the predetermined 3.5% non-inferiority margin set for the trial's primary endpoint in consultation with the US Food and Drug Administration (FDA).

Since then, several factors have contributed to the need for evaluation of different doses of sotrovimab. First, the development of the Omicron variant and its sublineages has caused the landscape to evolve substantially as described in the COVID-19 treatment guidelines from the NIH (COVID-19 Treatment Guidelines Panel 2022).

In the safety substudy, the aim will be to evaluate the safety and tolerability of sotrovimab across a single ascending dose level and over different infusion times when given for the treatment of mild/moderate COVID-19 to participants at high risk of disease progression. The existing non-clinical and clinical safety data support evaluation of sotrovimab across the range of doses in this sub study. The study will monitor for serious adverse events through Week 36. Additional information regarding data analysis is included in the statistical sections of this protocol and further details will be included in the statistical analysis plan (SAP).

2.2. Background

In December 2019, SARS-CoV-2, a novel betacoronavirus, was first reported to cause severe pneumonia in Wuhan, China and subsequently had a rapid spread around the world. As of May 2022, over 521 million cases of COVID-19 and over 6.3 million associated deaths have been reported globally, and over 82 million cases including over 999,000 deaths have been reported in the US (JHU 2022).

Sotrovimab is being developed for the prevention and treatment of COVID-19. Sotrovimab is a human IgG1κ mAb derived from the parental mAb S309, a mAb directed against the spike protein of SARS-CoV-1 that potently cross-neutralizes SARS-CoV-2, the causative agent of COVID-19 (Pinto 2020). Sotrovimab has an Fc modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. Sotrovimab binds with high affinity to the receptor binding domain of the SARS-CoV-2 spike protein. Sotrovimab retains neutralization activity in vitro against variants of concern and interest of the SARS-CoV-2 virus as defined by the World Health Organization, including, but not limited to, B.1.1.7 (Alpha, UK origin), B.1.351 (Beta, South Africa origin), P.1 (Gamma, Brazil origin), B.1.427/B.1.429 (Epsilon, California origin) B.1.526 (Iota, New York origin), B.1.617.1 (Kappa, India origin), B.1.617.2 (Delta, India origin), AY.1 (Delta Plus, India origin), AY.2 (Delta Plus, India origin), C.37 (Lambda, Peru origin), B.1.621 (Mu, Colombia origin), B.1.1.529/BA.1 (Omicron, South Africa origin), and B.1.1.529/BA.1.1 (Omicron, South Africa origin) (Cathcart 2022) variant spike proteins with fold-changes in half maximal effective concentration (EC_{50}) values of less than 5-fold as compared to wild-type spike. In vitro neutralization experiments indicate that sotrovimab neutralizes authentic Omicron BA.2 virus with a 15.7-fold change in EC_{50} value relative to wild-type (Cathcart 2022). Sotrovimab neutralized authentic Omicron BA.2 virus with a geometric mean EC_{90} value of 9476.3 ng/mL (range: 6796.8 to 14760.0 ng/mL; 35.1-fold change in EC_{90} value relative to wild-type) (PC-7831-0155).

Sotrovimab has been demonstrated to reduce hospitalization and/or death by 79% in non-hospitalized participants with mild to moderate COVID-19 who are at risk of progressing to severe disease when administered intravenously (IV) within 7 days of infection in a Phase 3 early treatment study COMET-ICE (Study VIR-7831-5001/GSK Study 214367) (Sotrovimab 2022). PK parameters are available from 9 participants in the Lead-in Phase of COMET-ICE. The geometric mean Cmax of 500 mg sotrovimab is 246 µg/mL (%CVb 39.4) following a 1-hr IV infusion. The estimated steady state volume of distribution is 7 L (%CVb 11.6) indicating limited distribution outside the vascular space. Sotrovimab has a geometric mean clearance of 90.3 mL/day (%CVb 25.2) and a median (min, max) half-life of 56.5 (42.4, 77.3) days.

2.2.1. Clinical Experience with Sotrovimab

As of 18 August 2021, a total of 1843 participants have received sotrovimab (500 mg dose) administered IV or intramuscularly in the Vir/GSK-sponsored clinical studies. Sotrovimab has been well tolerated when administered both intravenously and intramuscularly with no serious safety concerns identified to date. A summary of serious adverse event (SAE) and other safety data are included for these studies in the sotrovimab Investigator's Brochure.

Sotrovimab received Emergency Use Authorization in the US based on the results from COMET-ICE, a seamless FIH/Phase 2/3 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. Based on the results from COMET-ICE, temporary Authorizations have also been granted for sotrovimab in several countries, including Canada (Interim Order), Singapore (Pandemic Special Access), United Arab Emirates, Bahrain, Kuwait, Oman, Qatar, Thailand, and Brazil; provisional/conditional marketing approval has been granted in Australia, Saudi Arabia, United Kingdom, Japan and Switzerland; and full marketing approval has been granted in the European Union.

Other ongoing Vir/GSK-sponsored studies include a Phase 2 COMET-PEAK safety, PK, and virology study in early treatment (VIR-7831-5006/GSK Study 216912; NCT04779879), a Phase 3 COMET-TAIL study of intramuscular injection for early treatment (VIR-7831-5008), a Phase 2 study COMET-PACE study in pediatric participants for early treatment (VIR-7831-5005), and a Phase 1 pharmacokinetic (PK) study with healthy Japanese participants (VIR-7831-5009/GSK Study 217653; NCT04988152). In addition, Vir/GSK supported clinical studies (ACTIV-3-TICO [VIR-7831-5004, GSK Study 215149], BLAZE-4 [VIR-7831-5007, 217079]) are evaluating sotrovimab as a single agent or in combination. A summary of SAE and other safety data are included for these studies in the sotrovimab Investigator's Brochure (IB).

Sotrovimab at 1000 mg IV is also being evaluated in the UK-based RECOVERY platform trial, where hospitalized participants with confirmed COVID-19 are randomized to receive different candidate therapies. The RECOVERY Trial Independent Data Monitoring Committee's 04 March 2022 review of safety and efficacy data, inclusive of 568 participants that received 1 g IV sotrovimab, suggested no reason to modify the protocol.

To date, partial Gen 2 IV PK is available from BLAZE-4 (NCT04634409), COMET-PEAK (NCT04779879) and the Japan PK Study (NCT04988152).

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Sotrovimab		
Infusion reactions including hypersensitivity reactions (HSR)	While sotrovimab is a fully human IgG, Systemic reactions (SR), including hypersensitivity reactions, are a potential general risk associated with the mAb class of therapeutics. Given the totality of pre-clinical and clinical data to date it is the Sponsor's position that a up to 3000 mg dose may be safely used in individuals with mild to moderate COVID-19. There was no evidence of systemic infusion reactions in toxicology studies were conducted with sotrovimab in monkeys. Available safety data from the clinical development program comes from evaluation of a 500 mg dose of sotrovimab administered by IV infusion, a 500 mg and a 250 mg dose administered by IM injection for early treatment of COVID-19, and a 1000 mg dose currently being evaluated in an ongoing clinical study in hospitalized participants with severe COVID-19. Safety data from the clinical program to date have demonstrated a low rate of adverse events at the time of Day 29 analysis, particularly SAE and Grade 3-4 AEs. The COMET-ICE (Phase 2/3) and COMET-TAIL (Phase 3) studies demonstrated infrequent Grade 3 and 4 AEs and SAEs in the treatment groups. COMET-TAIL did not demonstrate a pattern of incrementing safety findings associated with increasing dose or exposure as it compared 250 mg IM to 500 mg IM and 500 mg IV dosing.	**Participant selection**: Participants will be excluded if they have a history of hypersensitivity to any of the excipients present in the investigational product. **Monitoring:** • During the Lead-In phase, participants will be monitored regularly at 15 minutes, 30 minutes, 45 minutes, 1 hour, and 2 hours post-administration of study treatment (including vital signs, see the SoA in Section 1.3). Post-infusion monitoring time will only be reduced to 1 hour for additional participants enrolled after the lead in phase is complete. • A Joint Safety Review Team (JSRT) review will be conducted at regular intervals, inclusive of active monitoring of lead-in data. ○ JSRT will review safety data before completing full cohort enrollment (after lead in phases), before any dose escalation (to review safety of the dose just prior to it) and before any decreases in infusion times (to review safety of the infusion time just prior to it)

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In the COMET-ICE study in participants with mild/moderate COVID-19 at high risk of progression, IRRs that occurred within 24 hours post infusion (pyrexia, chills, dizziness, dyspnea, pruritus, rash, and other 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 nonserious, 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 data cut-off. In COMET-ICE, all HSRs observed in the study were nonserious, 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 data cut-off. No anaphylaxis events were reported in the COMET-ICE study in participants with mild to moderate COVID-19 not requiring hospitalization at study entry. No anaphylaxis or serious hypersensitivity reactions were reported in the COMET-TAIL study in participants with mild to moderate COVID-19 not requiring hospitalization at study entry.	• Investigational product will be administered in the clinic with staff trained in emergency care and resuscitation procedures with emergency care kit on hand during the study intervention administration and post-therapy observation periods. • Investigators will be instructed to discontinue IV infusions for participants who develop Grade 3 or higher infusion reactions. • If a participant experiences a Grade 2 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 (eg, antihistamines, IV fluids). • Infusion-related reactions including HSRs will be categorized as AESIs (as has been done in the past for other studies).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 investigator to be related to study intervention. The participant was treated for the allergic reaction and recovered. Additional cases of anaphylaxis after dosing have been reported from post-marketing pharmacovigilance. The RECOVERY trial is a pragmatic platform clinical trial evaluating different treatments in hospitalized participants with serious COVID-19 and is currently ongoing in the UK. Given the pragmatic nature of the trial, limited safety data are collected during the course of the study with the focus being on SAEs that are believed to be related (with reasonable possibility) to the study treatment. RECOVERY is not a GSK/Vir sponsored trial, and therefore Vir does not currently have direct access to the blinded safety data from this study. However, a trial DMC letter dated 11 May 2022 noted that recruitment is ongoing and as of 2 May 2022, 996 participants had been randomized 1:1 (sotrovimab: standard of care). This trial DMC letter (dated 11 May 2022) also confirmed that review of safety data on 996 patients (1:1 sotrovimab: standard of care) was completed and that the trial may continue with no changes in conduct [DMC Report 2022]. The RECOVERY team has confirmed that up to the 21 March 2022 there has been only 1 related SAE reported. This was a case of suspected allergic reaction treated with adrenaline. The participant apparently improved within 2 hours without further complication and was discharged 5 days later.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Enhanced risk of systemic reactions including hypersensitivity reactions (SR/HSR) due to higher dose levels	See "Infusion reactions including hypersensitivity reactions (HSR)" It is possible that the risk of infusion reactions may be enhanced due to increase doses used, however as noted in the dose justification: the no-observed-adverse-effect-level for VIR-7831 was established when VIR-7831 was administered via IV infusion at 500 mg/kg (the highest dose tested) once a week for 2 weeks in cynomolgus monkeys (TX-7831-0102). Based on a preliminary population PK model for sotrovimab, the predicted AUC_{inf} following a 2000 mg IV dose is 21,400 µg*day/mL and predicted C_{max} is 636 µg/mL. Based on the proposed 2000 mg IV dose, the margins based on nonclinical Cmax and AUC margins of 21- and 10x, respectively, support the proposed clinical dose of 2 g IV. The AUC_{inf} following a 3 g IV dose is 32,100 µg*day/mL and predicted C_{max} is 954 µg/mL. Based on the proposed 3000 mg IV dose, the margins based on nonclinical Cmax and AUC margins of 14- and 7x, supporting the proposed doses up to 3000 mg.	See Mitigation Strategy for "Infusion reactions including hypersensitivity reactions (HSR)"
Enhanced risk of systemic reactions including hypersensitivity reactions (SR/HSR) due to decreased infusion times	See "Infusion reactions including hypersensitivity reactions (HSR)" It is possible that decreased infusion times in Cohort B1 (30-minute infusion time of 2000 mg) and B2 (15-minute infusion time of 2000 mg) may enhance the possibility of a systemic reaction including hypersensitivity reactions (SR/HSR)	See Mitigation Strategy for "Infusion reactions including hypersensitivity reactions (HSR)"

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunogenicity	While sotrovimab is a fully human 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.	**Monitoring:** This study will include participant follow-up for a period of 36 weeks to assess for the potential of immunogenicity (measurement of ADA) as well as if ADA is potentially causally associated with specific safety concerns and/or impact efficacy.
Antibody Dependent Enhancement (ADE) due to sub-neutralizing levels of sotrovimab enhancing fusion or leading to 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. ADE associated with Dengue virus 1-4 serotype infections is one of the most widely cited examples in which reinfection with a different serotype can, in a minority of participants, run a more severe course in the setting of limited antibodies generated by prior infection. The potential for enhanced disease in this setting is due to increased uptake of virus by FcR-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. As of 10 March 2021, the COMET ICE study enrollment has been stopped based profound efficacy on the recommendation of IDMC. The total of 1057 participants have been randomized to either the IV infusion of sotrovimab Gen1 (500 mg dose) or placebo. Based on the Joint SRT review of blinded data, there has been no confirmed events of ADE.	**Monitoring:** There is a safety lead in of 30 subjects for the initial 2000 mg and 3000 mg cohorts (Cohorts A and C) to aid in early detection of ADE. We recognize that ADE may not present until later time points, thus 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. Assessments for unusually severe disease in mAb-treated participants will be performed by the JSRT to assess for unusually severe disease in mAb-treated participants. Re-infection will be assessed as new SAEs related to COVID-19 infection during follow up period.

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 tissue [Hamming 2004], leading to tissue damage/immune complex disease This is hypothesized to have contributed to inflammation and airway obstruction observed in the small airways of infants who received a formalin-inactivated (FI) respiratory syncytial virus (RSV) vaccine [Polack 2002] and in a few cases of fatal H1N1 influenza infection [Wu 2010] The potential for enhanced disease in this setting may be due to low affinity or cross-reactive antibodies with poor or no neutralizing activity. 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. Observational data from 20,000 COVID-19 participants 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] Sotrovimab shows potent binding in vitro as well as neutralization of pseudovirus and live virus thus this risk is deemed to be low. In clinical studies to as of May 2022 there has been no evidence of ADE associated with sotrovimab.	**Monitoring:** 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. Periodic review of clinical signs and symptoms of COVID-19, clinical chemistry, AEs, end-organ disease and histopathological diagnoses will be performed by the JSRT to identify potential cases of immune complex disease. Assessments for unusually severe disease in mAb-treated participants will be performed by the JSRT. Re-infection will be assessed as new SAEs related to COVID-19 infection during follow-up period.

2.3.2. **Benefit Assessment:**

There is a biological rationale which supports the use of sotrovimab, an antiviral mAb in the early treatment of COVID-19 to prevent progression. Sotrovimab has been demonstrated in vitro to be a highly potent fully human IgG neutralizing SARS-CoV-2 antibody which has the potential to be an effective therapeutic in mild to critically ill participants with COVID-19. Sotrovimab does not bind to normal human tissues in a tissue cross-reactivity study and there were no adverse findings after 2 weeks in the 2-week repeat dose monkey toxicity study. The no -observed -adverse -effect-level (NOAEL) in the monkey study was 500 mg/kg, the highest dose tested.

Intravenous sotrovimab has been shown in a Phase 3 study (COMET-ICE) to be highly effective at preventing progression of mild/moderate COVID-19 when administered to participants who are at high-risk for severe disease. Furthermore, other anti-SARS-CoV-2 mAbs (bamlanivimab +/- etesevimab, casirivimab/imdevimab) have preliminarily been shown to decrease respiratory viral load and prevent progression to hospitalization or severe disease. (Chen 2020; Eli Lilly 2021; Weinreich 2021)

Available data suggest that SARS-CoV-2 infection is associated with variable incubation period, dependent on factors such as the infecting variant, patient risk group and vaccination status. Studies conducted from the first phase of the pandemic in 2020 describe the median incubation period as greater than five days [Lauer 2020]. Further studies looking at the Delta variant estimate this period to be four days [Grant 2022]. Whilst epidemiological studies on the Omicron variant are still ongoing, early research suggests the median incubation period for this variant is approximately three days [Brandal 2021; Helmsdal 2021; Jansen 2021]. The median time to progression to severe disease (ICU admission/development of acute respiratory distress syndrome) from onset of symptoms has been estimated to be 12 days (range 8 to 15 days) with a median duration from onset to death or discharge of 21 days (range 17 to 25 days) [Zhou 2020]. In addition, viral loads are highest early in the course of disease and tend to fall once severe sequelae have ensued, although remain detectable by RT-PCR well into the course of disease [Zhou, 2020; Wölfel, 2020]. The average duration of SARS-CoV-2 RNA shedding is estimated at 17·0 days in upper respiratory tract, 14·6 days in lower respiratory tract, 17·2 days in stool, and 16·6 days in serum samples [Cevik, 2021]. Notably, although viral nucleic acid can be detected well after symptom resolution in individuals with mild infection, shedding of infectious virus in sputum appears to be limited to the first week of symptoms [Wölfel, 2020].

These data suggest that early intervention with a potently neutralizing antibody prior to the onset of severe sequelae of disease may effectively prevent disease progression and hasten the resolution of disease. This study is warranted given that COVID-19 is considered a serious disease or condition - defined as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning, and that may lead to more severe complications.

Throughout the pandemic, the SARS-CoV-2 virus has continued to mutate, resulting in new variants. Some of these variants emerge and disappear while others persist. Because new variants will continue to emerge, this substudy is designed to collect clinical safety data at higher dose(s) of sotrovimab.

PPD

2.3.3. Overall Benefit: Risk Conclusion

The overall benefit-risk assessment considers the potential benefit of sotrovimab treatment through the potential ability to suppress viral replication and clear infected cells. The benefit in preventing the progression of mild to moderate non-hospitalized COVID 19 in high-risk participants has been demonstrated.

In addition, based on data from ~ 1200 non hospitalized and hospitalized subjects who have received IV infusion of sotrovimab in clinical studies performed by the sponsor, there have been no significant safety concerns observed as of 19-FEB-2022. Although there is a theoretical risk of ADE with anti-SARS-CoV2 mAbs in the presence of infection, no evidence of ADE with SARS-CoV-2 has been observed in the available literature to date.

In this safety substudy, participants will be closely monitored by medical monitoring and frequent JSRTs during this study. Safety will be monitored as described and decreases in infusion time will not be pursued unless it is agreed that there are no safety signals seen in previous cohorts.

The higher doses of sotrovimab tested in this study introduce the theoretical possibility of increased infusion related reactions and adverse events; however, the strong non-clinical profile with wide margins, and the robust safety profile of sotrovimab 500 mg across multiple clinical studies and 1000 mg in the RECOVERY study (without evidence of safety signals) suggest that higher doses will be beneficial to the population at need, with minimal risk.

Based on the unmet medical need and considering the measures taken to minimize risk to participants taking part in this study, the potential risks identified in association with sotrovimab are justified by the anticipated benefits that may be afforded to participants with mild to moderate COVID-19.

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3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Safety Describe the safety and tolerability up through Day 8 of high dose ascending intravenous sotrovimab	• Occurrence of adverse events (AEs) through Day 8 • Occurrence of serious adverse events (SAEs) through Day 8 • Occurrence of adverse events of special interest (AESIs) through Day 8 • Occurrence of disease related events (DREs) through Day 8
Secondary	
Safety Describe the safety and tolerability up through Week 36 of high dose ascending intravenous sotrovimab	• Occurrence of adverse events (AEs) through Week 12 • Occurrence of serious adverse events (SAEs) through Week 36 (end of study) • Occurrence of adverse events of special interest (AESIs) through Week 12 • Occurrence of disease related events (DREs) through Week 12
Safety Assess the immunogenicity up through Week 24 of high dose ascending intravenous sotrovimab	Incidence and titers (if applicable) of serum anti-drug antibody (ADA) and neutralizing antibody (if applicable) to sotrovimab through Week 24
Pharmacokinetics Assess the pharmacokinetics (PK) up to Week 24 of high dose ascending sotrovimab in serum following IV administration	IV sotrovimab pharmacokinetics (PK) in serum through Week 24
Exploratory	
Efficacy Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Hospitalization > 24 hours for acute management of illness due to any cause OR • Death
Efficacy Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR

Objectives	Endpoints
	• Hospitalization for acute management of illness for any duration and for any cause OR • Death
Efficacy Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of COVID-19 respiratory disease	Development of severe and/or critical respiratory COVID-19 as manifested by requirement for respiratory support (including oxygen) at Day 8, Day 15, Day 22, and Day 29
Efficacy Describe the effect of high dose ascending intravenous sotrovimab on the incidence of ICU stay and mechanical ventilation use through Day 29	Incidence of participants requiring ICU stay or mechanical ventilation through Day 29
Resistant Mutants Monitor SARS-CoV-2 resistant mutants against sotrovimab through Day 29	• SARS-CoV-2 resistance mutants to sotrovimab at baseline • Emergence of viral resistance mutants to mAb by SARS-CoV-2
Virologic Activity Evaluate the virologic activity of high dose ascending intravenous sotrovimab in reducing SARS-CoV-2 viral load through Day 29	• Change from baseline in viral load in nasal secretions by qRT-PCR during the follow-up period at Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29 • Undetectable SARS-CoV-2 in nasal secretions by qRT-PCR at Day 3, Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29 • Proportion of participants with a persistently high SARS-CoV-2 viral load at Day 8 by qRT-PCR

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4. STUDY DESIGN

4.1. Overall Design

The safety substudy is designed as a multi-center, open label substudy of high dose intravenous sotrovimab in participants with early, mild/moderate COVID-19 who are not on supplemental oxygen and are at risk for disease progression. Participants will receive an IV infusion of sotrovimab at different doses and infusion times (2000 mg infused over 60 minutes [planned], 30 minutes [optional] and 15 minutes [optional]) and up to 3000 mg (infused over 90 minutes [optional]) depending on which cohort the participant is enrolled in.

A total of up to 500 participants will be enrolled in this substudy and the cohorts will occur as outlined in the study schema (Section 1.2).

- Cohort A: Approximately 200 participants will be enrolled in Cohort A and receive 2000 mg of sotrovimab infused over 60 minutes.
    - 30 participants will be enrolled in a safety lead in, and relevant safety data through Day 8 will be reviewed by the Joint Safety Review Team (JSRT). Note, there will be no pause in Cohort A while the safety lead in data is reviewed.
    - 170 additional participants will then be enrolled to complete Cohort A. Enrollment will pause and a review of relevant safety data through Day 8 for these remaining participants in Cohort A will be performed by the JSRT. Looking at the totality of the data for 200 participants, the JSRT will make a safety assessment and a decision to open Cohorts B1 and/or C will be made.
- Optional Cohort B1: If a decision to proceed to Cohort B1 is made, approximately 50 participants will receive 2000 mg of sotrovimab infused over 30 minutes. The JSRT will then pause and review the relevant safety data through Day 8 from Cohort B1. Following the JSRT's safety assessment, a decision to open Cohort B2 will be made.
- Optional Cohort B2: If a decision to proceed to Cohort B2 is made, approximately 50 participants will be enrolled, and they will each receive 2000 mg of sotrovimab infused over 15 minutes. Review of relevant safety data through Day 8 will then be performed by the JSRT.
- Optional Cohort C: If a decision to proceed to Cohort C is made, approximately 200 participants will be enrolled in Cohort C, and they will each receive up to 3000 mg of sotrovimab, infused over 90 minutes. Note that this cohort may occur immediately after Cohort A.
    - 30 participants will be enrolled in a safety lead in, and relevant safety data through Day 8 will be reviewed by the JSRT. Note, there will be a pause in enrollment while relevant safety data through day 8 from the safety lead in group is reviewed.
    - 170 additional participants will then be enrolled into this cohort. The JSRT will then meet to review safety data through Day 8 from this complete cohort.

- If a lower dose than 2000 mg is selected for this cohort, there will be no safety lead-in for Cohort C and the infusion and monitoring times will be determined following safety review by the JSRT based on available safety data.

Cohorts B1, B2 and C will all be considered optional cohorts and can be opened following completion of the Cohort A safety assessment by the JSRT (B1 and C; B2 following JSRT safety assessment of B1).

After IV infusion, participants in the safety lead in Cohort A, and potentially Cohort C if a dose higher than 2000 mg is administered, will be monitored for 2 hours with vital signs assessments performed at 15 minutes, 30 minutes, 45 minutes, 1 hour and 2 hours. Participants in the remainder of Cohort A (and potentially Cohort C), Cohorts B1 and B2 will be monitored for up to 1 hour. As detailed in the Schedule of Activities, participants will be actively monitored on an outpatient basis with frequent collection of safety information through weekly in-clinic evaluations at Weeks 1, 2, 3, and 4, nasopharyngeal swabs for virology, and blood draws for PK sampling. Starting at Week 8, participants will be monitored monthly via phone call or in-clinic evaluation to assess for the incidence and severity of subsequent COVID-19 illness, if any, for a total of 36 weeks from dosing.

Number of Participants:

Approximately 200 participants (up to 500 with the optional cohorts) will be enrolled into this safety substudy.

In Cohort A of the safety substudy, 200 participants will be enrolled to receive a single 2000 mg IV infusion of sotrovimab over 60 minutes. Optional Cohorts B1 and B2 (in which participants will receive 2000 mg IV infusion of sotrovimab over 30 minutes and 15 minutes, respectively) will each enroll 50 participants.

Optional Cohort C (in which participants will receive up to 3000 mg IV infusion of sotrovimab over 90 minutes) will enroll 200 participants.

Intervention Groups and Duration:

Screening assessments in the safety substudy will be performed within 48 hours prior to randomization. There is no required minimum amount of time from screening to randomization provided that all eligibility criteria are met/confirmed.

Eligible participants will be treated with a single IV dose of 2000 or up to 3000 mg sotrovimab on Day 1 (depending on which cohort the participant is in) and followed for up to 36 weeks.

This is an open label study and all participants enrolled will receive sotrovimab treatment. Should multiple *optional* cohorts (i.e., Cohort B1 and Cohort C) be enrolling at the same time, participants will be randomly assigned to a cohort using a pre-defined schema.

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4.2. Scientific Rationale for Study Design

This study is a multi-center, open label study of high dose IV sotrovimab, a monoclonal antibody (mAb) against SARS-CoV-2 for the prevention of progression of mild/moderate COVID-19 in participants 18 years old and older at high risk of medical complications from COVID-19. High-risk adults include participants ≥55 years old regardless of co-morbidities and individuals age 18 or older with comorbidities associated with worse outcomes in adults, including diabetes, obesity (BMI ≥30), chronic kidney disease, congestive heart failure, chronic lung diseases (i.e. chronic obstructive pulmonary disease, moderate to severe asthma requiring steroids, interstitial lung disease, cystic fibrosis, and pulmonary hypertension), sickle cell disease, neurodevelopmental disorders, immunosuppressive disease or receiving immunosuppressive medications, or chronic liver disease (CDC 2021). The study will include participants infected with SARS-CoV-2, the virus that causes COVID-19, as confirmed by local laboratory tests and/or point of care tests.

Sotrovimab has been studied in a Phase 3 placebo-controlled trial evaluating the efficacy of sotrovimab in preventing progression of COVID-19 in high-risk participants with mild/moderate COVID-19 (VIR-7831-5001; COMET-ICE). On 10 Mar 2021, the independent data monitoring committee for COMET-ICE recommended that the study be stopped for enrollment due to evidence of clinical efficacy. This was based on an interim analysis of data from 583 participants which demonstrated an 85% (p=0.002) reduction in hospitalization or death in participants receiving sotrovimab compared to placebo (Vir 2021). Sotrovimab was well-tolerated with no safety signals detected.

The COMET-TAIL study was then designed to assess the efficacy, safety, and tolerability of intramuscular (IM) sotrovimab versus intravenous (IV) sotrovimab when given to high-risk participants for the treatment of mild/moderate COVID-19. This study evaluated the clinical efficacy of two dose levels of IM sotrovimab compared with IV sotrovimab in preventing progression of COVID-19 by utilizing a non-inferiority (NI) design. Enrollment was completed on 19-AUG-2021 and the day 29 analysis indicated the following: in the IM administration (500mg) arm of the trial, there was a 2.7% rate of progression to hospitalization for more than 24 hours or death through Day 29 of the trial, compared to 1.3% in the IV administration arm (also 500 mg). The adjusted difference between the IM and IV arms of the trial was 1.11% with a 95% confidence interval (CI) of -1.24% to 3.45%. The upper bound of the 95% CI was within the predetermined 3.5% non-inferiority margin set for the trial's primary endpoint in consultation with the US Food and Drug Administration (FDA).

Since COMET-ICE and COMET-TAIL, several factors have contributed to the need for evaluation of different doses of sotrovimab. First, the development of the omicron variant has caused the landscape to evolve substantially as described in the COVID-19 treatment guidelines from the NIH (COVID-19 Treatment Guidelines Panel 2022). Understanding the safety and tolerability of sotrovimab across a broader dose range will provide the data should a higher dose of sotrovimab be required to treat a variant that is less susceptible to sotrovimab in the future. Additionally, evaluation of sotrovimab across a range of doses will allow for additional clinical pharmacology evaluation of population PK parameters, including variability across different patient populations (vulnerable and pediatric populations). Adolescent and pediatric subjects will not be included in this study due to insufficient PK data in adult subjects at this time. Of note, the

COMET-PACE study in the pediatric population is currently ongoing to evaluate sotrovimab in this vulnerable population.

Thus, this study will now consist of two parts, the original protocol, and the safety substudy. In the safety substudy, the aim will be to evaluate the safety and tolerability of sotrovimab across a single ascending dose level and at different infusion times when given to high-risk participants for the treatment of mild/moderate COVID-19. The existing non-clinical and clinical safety data support evaluation of sotrovimab across a range of doses in this sub study.

Given the positive data from COMET-ICE and COMET-TAIL demonstrating clinical efficacy of sotrovimab in preventing COVID-19 disease progression, in addition to the existence of oral antivirals, and the changes in treatment guidelines noted above, enrollment to placebo is not ethically favorable for participants who are at risk of disease progression as it would unnecessarily subject participants to potential morbidity and mortality despite the availability of an otherwise favorable intervention. Thus, this study is designed as an open-label study with no formal inferential testing.

The primary endpoint is the occurrence of adverse events (AEs), serious adverse events (SAEs), occurrence of adverse events of special interest (AESIs) and occurrence of disease related events (DREs) through Day 8. Secondary endpoints include evaluations of safety and tolerability (AEs, AESIs and DREs through Week 12, and SAEs through Week 36), immunogenicity (incidence of ADA and neutralizing antibody), and assessment of PK.

The safety lead ins and pauses for JSRT review after completion of each cohort will allow for a closer safety analysis as the dose ascends during this study.

4.3. Justification for Dose

4.3.1. Sotrovimab

The IV doses (2000 mg or up to 3000 mg) selected for this substudy were chosen to establish safety and tolerability across a broad range to allow for flexible dosing options for future variants.

Based on clinical pharmacology modeling, a 2000 mg IV dose of sotrovimab is expected to maintain serum concentrations ≥120 µg/mL in 90% of participants for 28 days post-dose. These concentrations are ≥111 fold above WT tissue adjusted EC_{90} (assuming a lung: serum ratio of 0.25, measured value for sotrovimab) or ≥45 x $taEC_{90}$ (assuming lung: serum ratio of 0.10). Therefore, sotrovimab levels are expected to remain sufficiently above EC_{90} to provide adequate protection against variants such as BA.2 that confer moderate fold shifts in in vitro neutralization potency (BA.2 leads to 35-fold change in EC_{90}; geomean of Wisconsin and BEI isolates combined). A single dose of up to 3000 mg IV dose of sotrovimab would provide additional flexibility in the case that future variants with major shifts (>50) in EC90 arise. A single dose of up to 3000 mg IV dose is expected to maintain serum concentrations ≥180 µg/mL in 90% of participants for 28 days post-dose. These concentrations are ≥167 fold above WT tissue adjusted EC_{90} (assuming a lung: serum ratio of 0.25, measured value for sotrovimab) or >67 x $taEC_{90}$ (assuming lung: serum ratio of 0.10).

The no-observed-adverse-effect-level for VIR-7831 was established when VIR-7831 was administered via IV infusion at 500 mg/kg (the highest dose tested) once a week for 2 weeks in cynomolgus monkeys (TX-7831-0102). Based on a preliminary population PK model for sotrovimab, the predicted AUC_{inf} following a 2000 mg IV dose is 21,400 µg*day/mL and predicted C_{max} is 636 µg/mL. Based on the proposed 2000 mg IV dose, the margins based on nonclinical C_{max} and AUC margins of 21- and 10x, respectively, support the proposed clinical dose of 2 g IV. The AUC_{inf} following a 3 g IV dose is 32,100 µg*day/mL and predicted C_{max} is 954 µg/mL. Based on the proposed 3000 mg IV dose, the margins based on nonclinical C_{max} and AUC margins of 14- and 7x, supporting the proposed doses up to 3000 mg.

4.4. End of Study Definition

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

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5. STUDY POPULATION:

5.1. Inclusion Criteria

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

5.1.1. Age and Risk Factors

1. Participant must be aged 18 years or older at time of consent AND at high risk of progression of COVID-19 based on the presence of one or more of the following risk factors:
    a. For 18-54 years old: diabetes (requiring medication), obesity (BMI ≥ 30), chronic kidney disease (i.e., eGFR <60 by MDRD), congenital heart disease, congestive heart failure (NYHA class II or more), chronic lung diseases (i.e. chronic obstructive pulmonary disease, moderate to severe asthma requiring steroids, interstitial lung disease, cystic fibrosis, and pulmonary hypertension), sickle cell disease, neurodevelopmental disorders, immunosuppressive disease or receiving immunosuppressive medications, or chronic liver disease

OR

2. Participant ≥ 55 years old, irrespective of co-morbidities
    a. NOTE: Target approximately 20% of participants of the study population ≥ 65 years old

5.1.2. Type of Participant and Disease Characteristics

3. Participants who have a positive SARS-CoV-2 test result within 7 days of randomization (by any validated diagnostic test e.g., RT-PCR, antigen-based testing on any specimen type)

AND

4. Oxygen saturation ≥94% on room air

AND

5. Have symptoms of COVID-19 defined by one or more of the following: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhea, shortness of breath on exertion

AND

6. Participant to be dosed less than or equal to 7 days from onset of symptoms to dosing day (D1)

5.1.3. Sex and Contraceptive/Barrier Requirements

7. No gender restrictions
8. Female participants must meet and agree to abide by the following contraceptive criteria. Contraception use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

a. Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 Appendix 4: Contraceptive and Barrier Guidance Section 10.4.

OR

b. Is a WOCBP and using a contraceptive method that is effective or highly effective, as described in Section 10.4 of the protocol during the study intervention period and for up to 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.

A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention. See Section 8.3.7 Pregnancy Testing of the protocol.

– 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.

– Additional requirements for pregnancy testing during and after study intervention are located in Section 1.3 of the protocol.

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

5.1.4. Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

   OR

10. If participants are not capable of giving written informed consent, alternative consent procedures will be followed as described in Section 10.1.3.

5.2. Exclusion Criteria

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

5.2.1. Medical Conditions

1. Currently hospitalized or judged by the investigator as likely to require hospitalization for the treatment of COVID-19 in the next 24 hours
2. Symptoms consistent with severe COVID-19 as defined by new onset shortness of breath at rest or respiratory distress, or requiring hospitalization for continuous supplemental oxygen

3. Participants who, in the judgment of the investigator are likely to die in the next 7 days.
4. Known hypersensitivity to any constituent present in the investigational product

5.2.2. Prior/Concurrent Clinical Study Experience

5. Enrollment in any investigational vaccine study within the last 180 days or any other investigational drug study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer
6. Enrollment in any trial of an investigational drug, vaccine or device study for SARS-CoV-2/COVID-19 within 90 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer

5.2.3. Other Exclusions

7. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.
8. Participants who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol

5.3. Pre-Screening

Sites may have the option to pre-screen participants to participate in the clinical study. Sites may pre-screen and administer a SARS-CoV-2 test to participants who meet the Age and Risk Factor in Section 5.1.1, and display symptoms of COVID. Pre-screening is optional and not required by any site.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 serious adverse events (SAEs).

Re-screening may be performed as long as the participant is able to be dosed within 7 days after the onset of COVID-19 symptoms.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Overview of study interventions is provided in Table 3. Detailed instructions for the administration of study drug will be provided in a separate pharmacy manual.

Table 1: Overview of Study Intervention

Arm Name	**Sotrovimab IV**
Intervention Name	VIR-7831
Type	Biologic
Dose Formulation	Solution in single-use vial
Unit Dose Strength(s)	500 mg/vial (62.5 mg/mL)
Dosage Level(s)	2000 mg once or up to 3000 mg once
Route of Administration	IV infusion
IMP and NIMP	IMP
Sourcing	VIR-7831 will be provided centrally by the Sponsor.
Dosing instructions	See Pharmacy Manual
Special instructions	Gently mix VIR-7831 prior to withdrawing from vial
Packaging and Labelling	Study intervention will be provided in a single-use vial and labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	VIR-7831, GSK4182136

6.2. Preparation/Handling/Storage/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.

PPD

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 Sponsor study contact.

6.3. Randomization

This is an open label study and all participants enrolled will receive sotrovimab treatment. Should multiple *optional* cohorts (i.e., Cohort B1 and Cohort C) be enrolling at the same time, participants will be randomly assigned to a cohort using a predefined schema.

6.4. Study Intervention Compliance

Participants will receive sotrovimab IV directly from the investigator or designee, under medical supervision. The date and start and stop times of the dose administered will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

Dose modifications are not applicable. See Section 7.1 for instructions to discontinue study treatment for safety reasons.

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

COVID-19 is an acute illness and participants are not expected to need continued access to sotrovimab after the end of the study.

6.7. Treatment of Overdose

No specific treatment is recommended for an overdose. The treatment 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 AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6.8. Concomitant Therapy

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

1. Reason for use
2. Dates of administration including start and end dates

3. Dosage information including dose and frequency

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

1. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb is not permitted during the study unless these are given as local standard of care if a participant is hospitalized.
2. Receipt of antivirals against COVID-19, including Paxlovid, molnupiravir, remdesivir, or passive antibody therapies are not permitted for the duration of the study unless these are given as local standard of care.
3. Receipt of investigational treatments is not permitted for the duration of the study.
4. Vaccination against COVID-19 will not be allowed 1 week prior to dosing and 8 days after dosing.

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.

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

PPD

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant will be permanently discontinued from completion of drug infusion if they experience a life-threatening, infusion-related reaction including severe allergic or hypersensitivity reactions, severe cytokine release syndrome.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for follow-up assessments. See the Schedule of Activities in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

If a participant experiences a mild allergic or hypersensitivity reaction, the investigators will be instructed to pause the infusion. The infusion may be restarted at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids).

7.2. Participant Discontinuation/Withdrawal from Study

- A participant may withdraw from the study at any time at his/her own request, at the request of their LAR (legally authorized representative) 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 Schedule of Activities (Section 1.3). Participants may be contacted by phone. See Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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 return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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.

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

8. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment.

1. Study procedures and their timing are summarized in Section 1.3 (Schedule of Activities).
2. Select follow-up visits as noted in the Schedule of Activities are planned to be phone calls from site to participants. Follow-up visits may be performed at the clinic or as a home visit.
3. Protocol waivers or exemptions are not allowed.
4. Immediate safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
5. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
6. 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. Re-screening may be performed as long as the participant is able to be dosed within 7 days after the onset of COVID-19 symptoms.
7. Procedures conducted as part of the participant's routine clinical management (e.g., blood count and COVID-19 testing) and obtained before signing of 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 Schedule of Activities.
8. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
9. Clinical Research Associates will review the participants' records to verify that prioritized 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 records.

8.1. Screening Period

Informed consent must be obtained before conducting any study procedures. Screening will be performed within 48 hours prior to randomization and include the assessments outlined in the Schedule of Activities (Section 1.3).

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

8.1.1. 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.

PPD

8.1.2. SARS-CoV-2 Diagnostic Testing

Documentation of laboratory-confirmed SARS-CoV-2 infection via a validated molecular diagnostic test or antigen test from any respiratory specimen collected ≤ 7 days prior to study entry must be confirmed for eligibility. This can include tests conducted in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent or from a diagnostic test that has received an Emergency Use Authorization from the FDA (FDA 2022).

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.

8.1.3. Secondary Contact Information

In order to minimize the potential for missing data related to the primary endpoint 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 clinic visit, home visit, and during site phone calls.

8.2. Efficacy Assessments

8.2.1. Hospitalization and Death Data Collection

A hospitalization event and the clinical care that is received during a hospitalization as well as death are components of primary, secondary, and exploratory endpoints. Data from the hospitalization and/or death should be captured in the electronic data capture (EDC) system including but not limited to:

1. Serious Adverse Event (SAE) form
2. Dates that the participant is hospitalized and discharged
3. Dates that the participant is admitted to an intensive care unit
4. Details on the amount of and type of supplemental oxygen and/or ventilatory support that the participant received
5. Date, time, and cause of death

8.2.2. Phone Call for Subsequent COVID-19 Illness

To monitor participants for subsequent COVID-19 illness after Day 29, participants will be called at Week 8, Week 16, Week 28, Week 32, and Week 36 (as they don't have to come in for a clinic visit on these days). 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 because of this illness will also be recorded.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.3.1. Physical Examinations

A complete physical examination will be performed on Day 1. For all other visits the physical examination will be symptom-directed as outlined in the Schedule of Activities.

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, and Abdominal systems.
- Height and weight will also be measured and recorded at Screening. Body mass index (BMI) will be calculated from these measurements.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

On Day 1, vital signs should be recorded prior to dose administration and at 15 mins, 30 mins, 45 mins, 1 hour and 2 hours after infusion for participants who are part of the lead in, and for 15 mins, 30 mins, 45 mins and 1 hour after infusion for participants who are not part of the lead in.

- Vital sign measurements will include blood pressure, pulse rate, temperature (oral preferred), respiratory rate, and oxygen saturation.
- Blood pressure and pulse measurements will be assessed while participant is semi-supine or sitting with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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).

8.3.3. Electrocardiograms

At Screening, a single 12-lead ECG is required ONLY for participants with past medical history of a cardiovascular condition such as an arrhythmia, coronary artery disease, congestive heart failure, valvular disease, OR diabetes mellitus.

Electrocardiograms will be performed locally as outlined in the Schedule of Activities (see Section 1.3). 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.

8.3.4. Virologic Measures

Samples for virological analysis will be collected in accordance with the laboratory manual and Schedule of Activities (Section 1.3).

- Nasopharyngeal swabs will be collected for SARS-CoV-2 RT-PCR

- Samples may also be used for resistance surveillance analysis
- Day 1 samples may be used to evaluate for other respiratory infections

8.3.5. Resistance Analyses

To monitor for viral resistance, resistance surveillance will be conducted for all participants who are randomized and dosed. Next-generation sequencing (NGS) analysis of the SARS-CoV-2 spike gene will be attempted to identify substitutions in the mAb epitope or substitutions outside of the epitope that arise during treatment. NP samples from baseline and the last evaluable post-baseline visit at Day 5 or later will be subjected to NGS analysis, including participants who do not experience a decline in viral load or who experience virologic rebound. Virologic rebound will be defined as participants who experience an increase of >1 $\log_{10}$ copies/mL in viral load, or viral load becomes quantifiable after having been below the limit of quantification. For identified substitutions that qualify for phenotypic analysis, in vitro phenotypic analysis of the antiviral activity of sotrovimab using a SARS-CoV-2 spike pseudotyped virus system will be attempted and analyzed for reduced susceptibility to sotrovimab.

8.3.6. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.
- Laboratory assessments at Screening visit will be performed locally at the clinical site as determined necessary by the investigator or as required by local regulations.
- All protocol-required laboratory test performed locally and/or centrally, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and Schedule of Activities (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 by the investigator to be clinically significantly abnormal during participation in the study 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 of time 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.

8.3.7. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at Screening to confirm eligibility and at Week 24 or Early Withdrawal visit. If serum pregnancy test is required, it will be performed locally.
- Additional serum or 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.

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

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3.

The definitions of unsolicited and solicited adverse events 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 legally authorized representative).

Hospitalization or death are typically considered SAEs and they are included in the primary endpoint. However, if a hospitalization or adverse event is related to expected progression, signs, or symptoms of COVID-19 (as detailed in Section 8.4.8) or if hospitalization is due to elective treatment of a pre-existing condition that did not worsen from baseline as noted in Section 10.3 it will not be considered as an SAE. These events will be collected and reported as SAEs only if the event is more severe than expected for the participant's current clinical status and medical history or if the investigator feels that it is related to study drug. These will be collected and reported as SAEs as delineated in Section 8.4.1 below. Since it will not be possible to delineate in a single participant whether the hospitalization is directly related to COVID-19 complications or could be related to sotrovimab causing more severe disease due to ADE, all hospitalizations for management of acute illness, regardless of cause, will be included in the primary endpoint.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting 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). As noted in Section 8.2.1 data on hospitalization or death should additionally be recorded in the eCRF for all relevant sections.

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.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs will be collected from dose administration through Week 12 post-dose. SAEs will be collected from dose administration through the Week 36 follow-up visit at the time points specified in the Schedule of Activities (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated

procedure, invasive tests or change in existing therapy) will be recorded from the time the participant consents to participate in the study.

- 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 or designee 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 or designee.

8.4.2. 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.

8.4.3. Method of Detecting AEs and SAEs

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.

8.4.4. 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 non-serious AEs of special interest (as defined in Section 8.4.8), 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.

8.4.5. Regulatory Reporting Requirements for SAEs

PPD and GlaxoSmithKline (GSK) are acting on behalf of Vir for the purposes of global safety reporting for this study as outlined in the PPD/Vir Safety Medical Management Plan and Expedited Safety Reporting Documents.

- Prompt notification by the investigator to PPD 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 or designee has a legal responsibility to notify both the local regulatory authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor or designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review

Boards (IRB)/Independent Ethics Committees (IEC), and investigators. Details for notification of expedited and periodic safety reporting can be found in the Expedited and Periodic Safety Reporting Plan (ESRP).

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) as outlined in the ESRP will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.4.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until Week 36.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to sponsor or designee within 24 hours of learning of the female participant 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 and for up to 1 year after birth. The investigator will collect follow-up information on the participant and the neonate/child, and the information will be forwarded to the sponsor or designee.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor or designee as described in Section 8.4.1. 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.

8.4.7. Cardiovascular and Death Events

Specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed for all deaths and cardiovascular events detailed in Section 8.4, whether these events are considered SAEs or not. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

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8.4.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or 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, or resulting in hospitalization as noted in Section 8.4, 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 patient'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 and that should be considered as expected progression, signs, or symptoms of COVID-19:

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

8.4.9. Adverse Events of Special Interest

Adverse events of special interest are defined as relevant known toxicities of other therapeutic mAbs or are defined from signals observed in previous studies in the nonclinical or clinical sotrovimab programs, that the sponsor will monitor throughout the study. AESIs may be updated during the study based on accumulating safety data.

Adverse events of special interest include:

- Infusion-related reactions including hypersensitivity reactions within 24 hours after infusion
- Hypersensitivity reactions occurring at any time post dose
- Immunogenicity related AEs
- Adverse events potentially related to ADE of disease. Antibody-dependent enhancement theoretically can occur via 1 of 3 previously described mechanisms described in Section 8.4.9.3.

8.4.9.1. Systemic Reactions and Hypersensitivity Reactions

Please refer to local or institutional guidelines for monitoring relevant adverse events encompassing infusion related reactions including hypersensitivity, angioedema, anaphylaxis,

acute anaphylactic shock and minor allergic episodes. Premedications will be permitted at the investigator's discretion and will be appropriately documented.

8.4.9.2. Immunogenicity

Unwanted immunogenicity is an immune response by an organism against a therapeutic protein. This reaction leads to production of anti-drug-antibodies (ADA) which may inactivate the therapeutic effects of the treatment and, in rare cases, induce adverse events. This study will include participant follow-up for a period of 5 half-lives to assess for the development of ADA and potential impacts on safety, PK and/or efficacy.

8.4.9.3. Antibody Dependent Enhancement

Antibody-dependent enhancement (ADE) of disease theoretically can occur via one of three previously described mechanisms:

1. By facilitating viral entry into host cells and enhancing viral replication in these cells
2. By increasing viral fusion with target host cells, enhancing viral replication in these cells
3. 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 5 half-lives 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 temporally associated with sotrovimab dosing or as increased severity or duration of illness in sotrovimab-treated participants vs. placebo-treated participants.

As of 10 March 2021, enrollment into the COMET ICE study, evaluating sotrovimab for the treatment of non-hospitalized individuals with mild to moderate COVID-19, has been stopped based on the recommendation of IDMC. The total of 1057 participants have been randomized to either the IV infusion of sotrovimab Gen1 (500 mg dose) or placebo. Based on the Joint SRT review of blinded data, there has been no confirmed events of ADE. The ACTIV-3 TICO study of sotrovimab treatment in hospitalized participants with COVID-19 symptoms, which was terminated due to futility, did not reveal any safety concerns overall and no ADE. The COMET TAIL study did not reveal any safety concerns overall and no ADE.

As described in Section 2.3.1, AEs potentially related to ADE of the disease will be reviewed by the JSRT to see if there are unusually severe manifestations of COVID-19 in treated individuals.

8.5. Pharmacokinetics

Blood samples for serum PK will be collected as detailed in the Schedule of Activities (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.

PPD

- 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 for sotrovimab, one sample of sufficient volume can be used.

Serum concentrations may be combined with data from other studies evaluating sotrovimab for the purpose of population PK model development. Pharmacokinetic analyses may be conducted to explore exposure-response relationships between PK parameters and selected antiviral variables. 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 analysis plan.

8.6. Immunogenicity Assessments

Antibodies to sotrovimab will be evaluated in serum samples collected from all participants according to the Schedule of Activities (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 designee.

Serum samples will be screened for antibodies binding to sotrovimab and the titer of confirmed positive samples will be reported. 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. All samples collected for detection of antibodies to study intervention will also be evaluated for sotrovimab serum concentration 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). 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.

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of the study is to describe the safety and tolerability of high dose ascending intravenous sotrovimab administered over different infusion times. No formal statistical hypothesis testing is planned.

9.2. Sample Size Determination

A sample size of approximately 200, and up to 500 participants (with 300 participants designed to be included through optional cohorts as determined by the Joint Safety Review team (JSRT)) was selected to assess the safety profile of an increased dose of sotrovimab robustly and efficiently. Adverse events with a frequency of ≥ l% and < 10% are considered common/frequent as per the 2nd edition of the CIOMS Working Groups III and IV (CIOMS 1999).

The first cohort, Cohort A, will include approximately 200 participants dosed at 2000 mg IV with an infusion time of 60 minutes. With 200 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 1.14%. Of note, in COMET-ICE, the infusion related reaction (IRR) rate was 1.14%.

Cohort B1 is optional and can occur after Cohort A if there are no significant safety signals or concerns found in Cohort A. It would include approximately 50 participants dosed at 2000 mg with an infusion time of 30 minutes. With 50 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 4.5%.

Cohort B2 is optional and can occur after Cohort B1 if there are no significant safety signals or concerns found in Cohort A or B1. It would include approximately 50 participants dosed at 2000 mg with an infusion time of 15 minutes. With 50 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 4.5%.

Cohort C is optional and can occur after Cohort A if there are no significant safety signals or concerns found in Cohort A. It would include approximately 200 participants dosed at up to 3000 mg IV with an infusion time of 90 minutes (if 3000 mg IV is selected). With 200 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 1.14%.

Cohorts B1, B2 and C will all be considered optional cohorts and will be opened following completion of Cohort A following assessment by the JSRT.

The precision of event rate estimation is shown in the table below, as indicated by the width of 95% confidence intervals. More specifically, the total number of 500 participants reflects the precisions when summarizing over all cohorts, and the total number of 300 participants reflects the precisions when summarizing over all 2000 mg cohorts.

Table 2: Precision of Estimated Event Rate

Total Number of Participants	Number of Participants with a Particular Event	Event Rate	95% Confidence Interval
500 (overall study size, including Cohorts A, B1, B2, and C)	3	0.5%	(0.12%, 1.74%)
	5	1.0%	(0.33%, 2.32%)
	10	2.0%	(0.96%, 3.65%)
	25	5.0%	(3.26%, 7.29%)
	50	10.0%	(7.51%, 12.97%)
	250	50.0%	(45.53%, 54.47%)
300 (combined number of participants dosed at 2000 mg, includes Cohorts A, B1 and B2)	2	0.5%	(0.08%, 2.39%)
	3	1.0%	(0.21%, 2.89%)
	6	2.0%	(0.74%, 4.30%)
	15	5.0%	(2.83%, 8.11%)
	30	10.0%	(6.85%, 13.97%)
	150	50.0%	(44.20%, 55.80%)
200 (individual study size for Cohorts A or C)	1	0.5%	(0.01%, 2.75%)
	2	1.0%	(0.12%, 3.57%)
	4	2.0%	(0.55%, 5.04%)
	10	5.0%	(2.42%, 9.00%)
	20	10.0%	(6.22%, 15.02%)
	100	50.0%	(42.87%, 57.13%)
50 (individual study size for cohorts B1 or B2)	0	0.5%	(0.00%, 7.11%)
	1	1.0%	(0.05%, 10.65%)
	1	2.0%	(0.05%, 10.65%)
	3	5.0%	(1.25%, 16.55%)
	5	10.0%	(3.33%, 21.81%)
	25	50.0%	(35.53%, 64.47%)

9.3. Analysis Sets

For the purposes of analysis, the following main analysis sets are defined:

Participant Analysis Set	Description
Safety	All participants who were enrolled and exposed to study intervention. Participants will be summarized according to actual dose and infusion time received during the study.
Intent-to-Treat (ITT)	All participants who were randomized and exposed to study intervention. Participants will be summarized according to the dose they were assigned to.
Pharmacokinetic	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (post-dose non-quantifiable [NQ] values will be considered as non-missing values). Participants will be summarized according to treatment which they received.
Virology	All participants who were enrolled and with a lab confirmed quantifiable nasopharyngeal swab at Day 1. Participants will be summarized according to actual dose received during the study. This will be the primary analysis set for virology.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to formal reporting of Cohort A for the sub-study and it will include a more detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the safety endpoints. All statistical analyses will be descriptive. The details of the descriptive summary statistics will be outlined in the statistical analysis plan.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the statistical analysis plan. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.1. Primary Endpoints

The primary objective of the safety substudy is to describe the safety and tolerability through Day 8 of high dose ascending intravenous sotrovimab. Summaries of AEs, SAEs, AESI, COVID-related AEs through Day 8 will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE will be counted once.

In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

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9.4.2. Secondary Endpoint(s)

Details of the analyses for the secondary endpoints will be provided in the statistical analysis plan.

9.4.3. Exploratory Endpoint(s)

Details of the analyses for the exploratory endpoints will be provided in the statistical analysis plan.

9.4.4. Other Safety Analysis

Number and percentage of subjects with AEs, SAEs, COVID-19 related AEs and COVID-19 related SAEs, and AESIs beyond Day 8, including laboratory tests and vital signs will be displayed in the form of listings, frequencies, summary statistics, and graphs where appropriate. Interpretation will be aided by clinical expertise.

To inform on the number and nature of non-COVID-19 adverse events and serious adverse events, additional safety analyses will be performed in which select, pre-specified terms consistent with known progression of COVID-19 disease will be excluded. Details of these and all analyses, including example outputs, will be documented in the statistical analysis plan.

9.4.5. Other Analysis

Full details of all analysis methods of immunogenicity and population pharmacokinetics will be provided in the statistical analysis plan.

9.5. Interim Analysis

No interim analyses are planned. Note that the JSRT will review the safety and tolerability data from each cohort when all subjects in a cohort have completed Day 8. The details of the safety data review through Day 8 will be outlined in the statistical analysis plan.

9.6. Multiple Comparisons and Multiplicity

No statistical testing will be conducted in the safety substudy.

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, EU Clinical Trials Directive 2001/20/EC or Regulation (EU) No. 536/2014 (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor or designee with sufficient, accurate financial information as requested to allow the sponsor/designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and sub-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 Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A signed copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Vir (alone or working with others) may use the participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about sotrovimab or about the study disease; fulfill legal and regulatory obligations, including reporting safety information about sotrovimab, this study, and the results of this study to regulatory authorities; provide information about the safety and use of sotrovimab to investigators and institutions that plan to administer sotrovimab to participants; publish the results of these research efforts; work with government agencies or insurers to have sotrovimab approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor/designee. Any participant records or datasets that are transferred to the sponsor/designee will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor/designee 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 their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor/designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Joint Safety Review Team

A Joint Safety Review Team (JSRT) comprised of team members from clinical research, pharmacovigilance and statistics from Vir and GSK will meet at regular intervals throughout the conduct of the study for review of instream safety data for identification of safety concerns. If a potential safety issue is identified, the JSRT may escalate this to an ad hoc IDMC meeting for further evaluation.

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 trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- Sponsor or its designee will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- 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.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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 the 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.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, 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.
- As hospitalization and mortality are both primary study endpoints and serious adverse events, instream data cleaning including updating and reconciliation of hospitalization events between the safety dataset and efficacy dataset will be performed throughout the study duration and any changes or updates to the SAEs of hospitalization or mortality will be reflected in the efficacy dataset.

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 printed CRFs or entered in the electronic eCRFs 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 [Investigator Source Data Agreement].
- 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

10.1.9.1. First Act of Recruitment

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

10.1.9.2. Study/Site Termination

Vir reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of Vir. 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(s) 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 3 will be performed by the central laboratory and/or the site local laboratory

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

Table 3: Protocol-Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	<u>WBC count with Differential</u>: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine [1]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	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)	
Pregnancy testing	Highly sensitive (Serum/plasma or urine) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			

[1] Repeat within 1 week if above the normal range

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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 adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant 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 health care provider). The participants 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 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 participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined such as infusion reactions and systemic events for which the participant is specifically questioned.

Events Meeting the AE Definition

- 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.
- Clinically significant changes in laboratory assessments.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Elective treatment of a pre-existing condition that did not worsen from baseline. • 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 serious adverse event that, at any dose:
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 • 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. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any serious adverse event that, at any dose:
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 medically significant 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. o 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: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

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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.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by pharmacovigilance staff. 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.
- 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

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, 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.

- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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) and/or Product Information, for marketed products, 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.

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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 sponsor. 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 sponsor.** • 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.

10.3.5. Reporting of SAEs

SAE Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting SAEs will be the electronic data collection (EDC) tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours. Details to be provided in the Study Specific SAE Reporting Guidelines. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 24 hours of SAE entry into the eCRF. • 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 SAE coordinator by telephone. • Contacts for SAE reporting will be included in the Study Specific SAE Reporting Guidelines

10.3.6. Expedited Reporting to Health Authorities, Investigators and Ethics Committees

Expedited Reporting
The Sponsor or their third-party delegates will promptly evaluate all serious adverse events and non-serious adverse events to identify and expeditiously communicate new safety findings to investigators, IRBs, ECs, and health authorities based on applicable legislation as per the Expedited and Periodic Safety Reporting Plan. To determine reporting requirements for single adverse event cases, the Sponsor or their third-party delegate will assess the expectedness of these events using the sotrovimab Investigator's Brochure.

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10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

10.4.1.1. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L or mIU/mL) is required.
- Females on HRT and whose menopausal status is in doubt and in whom highly effective methods are contraception are required will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.1.2. Woman of Childbearing Potential (WOCBP)

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

3. Following menarche
4. From the time of menarche until becoming postmenopausal or premenopausal with permanent infertility (see above)

Note: 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 (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

PPD

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[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• Bilateral tubal occlusion, bilateral tubal ligation, or bilateral salpingectomy
• Azoospermic partner (vasectomized or due to a medical cause) 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. 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 – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *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.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide

Contraceptives[a] Allowed During the Study Include:
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

[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] Male condoms must be used in addition to hormonal contraception. 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.
[d] Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
[e] Male condom and female condom should not be used together (due to risk of failure from friction).

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