Protocol

Study ID: 217653

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

IND Identifier: 149315

Date of Document: 27-MAY-2021

TITLE PAGE

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Protocol Number: GSK Study 217653 (VIR-7831-5009)

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

Brief Title: A Phase I single-dose study to investigate the pharmacokinetics, safety, and tolerability of sotrovimab vs placebo by intravenous or intramuscular administration in healthy Japanese and Caucasian participants

Study Phase: Phase I

Sponsor Name and Legal Registered Address:

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158
USA

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

Regulatory Agency Identifying Number(s):

IND: 149315

Approval Date: 27-MAY-2021

SPONSOR SIGNATORY:

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Elizabeth Alexander MD, MSc, FIDSA
Senior Director, Clinical Research (Vir)

Date

The signed page is a separate document.

Medical Monitor Name and Contact Information will be provided separately

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Brief Title: A Phase I single-dose study to investigate the pharmacokinetics, safety, and tolerability of sotrovimab vs placebo by intravenous or intramuscular administration in healthy Japanese and Caucasian participants

Rationale:

Sotrovimab is being developed for treatment as well as for prophylaxis of Coronavirus disease 2019 (COVID-19). Sotrovimab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) derived from the parental mAb S309, a mAb directed against the spike protein of severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) that potently cross-neutralizes SARS-CoV-2, the causative agent of COVID-19. The Fc domain of sotrovimab includes the 2 amino acid "LS" modification that extends antibody half-life and is also expected to enhance distribution to the respiratory mucosa. Previous clinical experience has been gained in ongoing studies of sotrovimab as a treatment for participants with mild to moderate COVID-19 (COMET-ICE [NCT04545060], BLAZE-4 [NCT04634409], COMET-PEAK [NCT04779879], and COMET-TAIL [VIR-7831-5008; GSK Study 217114]) and in hospitalized participants with COVID-19 (ACTIV-3-TICO [NCT04501978]).

This study is the first study in healthy Caucasian and Japanese participants. The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single fixed dose of sotrovimab administered intravenously or via intramuscular (IM) injection in Japanese and Caucasian healthy volunteers. These routes of administration were selected because of demonstrated efficacy of the intravenous (IV) route in early treatment of mild-to-moderate COVID-19 at high risk for progression, and to treat patients who lack access to IV infusion centers with IM injections; these are also the intended routes of administration for registration. The data from this study will be used to supplement data available from other clinical trials that were conducted in non-Japanese participants, will offer an opportunity for direct comparison of healthy Japanese to healthy Caucasian participants, and will support dose selection in Japan.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Pharmacokinetics (Part 1) To assess the PK of sotrovimab administered via IV infusion in healthy	PK parameters through Day 29: maximum observed serum concentration (C_{max}), area under the serum-concentration time curve from Day 1 to

Objectives	Endpoints
Japanese and Caucasian participants through Day 29	Day 29 (AUC_{D1-29}), time to C_{max} (T_{max}), and concentration at Day 29 (C_{D29}) of sotrovimab, as data permits.
Pharmacokinetics (Part 2) To assess the PK of sotrovimab administered via IM injections in healthy Japanese and Caucasian participants through Day 29	PK parameters through Day 29: C_{max}, AUC_{D1-29}, T_{max}, and C_{D29} of sotrovimab, as data permits.
Safety (Part 1) To evaluate the safety and tolerability profile of IV sotrovimab in healthy Japanese and Caucasian participants through Day 29	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29 • Occurrence of adverse events of special interest (AESIs) through Day 29 • Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29 • Occurrence of clinically significant changes in vital signs compared to Baseline[a] through Day 29 • Occurrence of clinically significant laboratory abnormalities through Day 29
Safety (Part 2) To evaluate the safety and tolerability profile of IM sotrovimab in healthy Japanese and Caucasian participants through Day 29	• Occurrence of AEs through Day 29 • Occurrence of SAEs through Day 29 • Occurrence of AESIs through Day 29 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Day 29 • Occurrence of clinically significant changes in vital signs compared to Baseline[a] through Day 29 • Occurrence of clinically significant laboratory abnormalities through Day 29
Secondary	
Pharmacokinetics (Part 1) To assess the PK of sotrovimab administered via IV infusion in healthy Japanese and Caucasian participants	PK parameters through Week 18: C_{max}, area under the serum concentration-time curve extrapolated to infinite time (AUC_{inf}), area under the curve from the time of dosing to the time of the last measurable (positive) concentration

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

[a] Baseline is defined as assessments performed following admission to unit on Day -1 and before dosing on Day 1.

Overall Design:

This study is a randomized, multi-center, placebo-controlled, single-blind, single-dose, parallel group Phase I trial to assess the PK of IV and IM sotrovimab in healthy Japanese and Caucasian participants. This study will occur in two parts (Part 1 and Part 2).

Part 1:

Healthy Japanese and Caucasian participants will be randomized in a 4:1 ratio to receive a single, 500 mg IV infusion of sotrovimab or volume-matched saline placebo. Eligible participants will be treated with a single IV dose of sotrovimab or volume-matched saline placebo on Day 1. Participants will be blinded to study intervention. Safety, tolerability, immunogenicity, and PK of IV sotrovimab will be evaluated.

Part 2:

Part 2 will begin after enrollment has been completed for Part 1. Healthy Japanese and Caucasian participants will be randomized in a 4:1 ratio to receive a single, 500 mg IM dose of sotrovimab or volume-matched saline placebo. Eligible participants will be treated with a single IM dose of sotrovimab or volume-matched saline placebo (given as two 4 mL injections, one in each dorsogluteal muscle) on Day 1. Participants will be blinded to study intervention. Safety, tolerability, immunogenicity, and PK of IM sotrovimab will be evaluated.

Brief Summary:

The purpose of this study is to assess the safety, tolerability, immunogenicity, and PK of IV and IM sotrovimab in healthy Japanese and Caucasian participants. The primary endpoints are PK and safety through Day 29.

- Study Duration: 18 weeks after dosing. Participants can be screened up to 28 days before dosing, leading to a maximum study duration of 22 weeks.
- Treatment Duration: A single dose of sotrovimab or equal volume saline-placebo will be administered by IV infusion or administered IM (IM dose is administered as two 4 mL injections, one in each dorsogluteal muscle) on Day 1.
- Visit Frequency: Participants will be admitted to the clinical research unit on the day prior to study drug administration (Day -1) and will remain in the unit until all Day 3 study activities are completed. Participants will need to return to the study site for 7 follow-up visits during the 18 week study (at Weeks 2, 3, 4, 6, 8, 12, and 18).

Number of Participants:

If participants permanently discontinue the study before Day 29 additional participants may be enrolled as replacements and assigned to the same cohort (i.e., Part 1 or Part 2) and treatment at the discretion of the Sponsor or designee in consultation with the investigator.

Part 1:

A maximum of 24 participants will be randomized in Part 1 to achieve 20 evaluable participants in Part 1. The Part 1 cohort will enroll approximately 8 Japanese and 8 Caucasian participants to the IV sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm.

Part 2:

A maximum of 24 participants will be randomized in Part 2 to achieve 20 evaluable participants in Part 2. The Part 2 cohort will enroll approximately 8 Japanese and 8 Caucasian participants to the IM sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm.

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

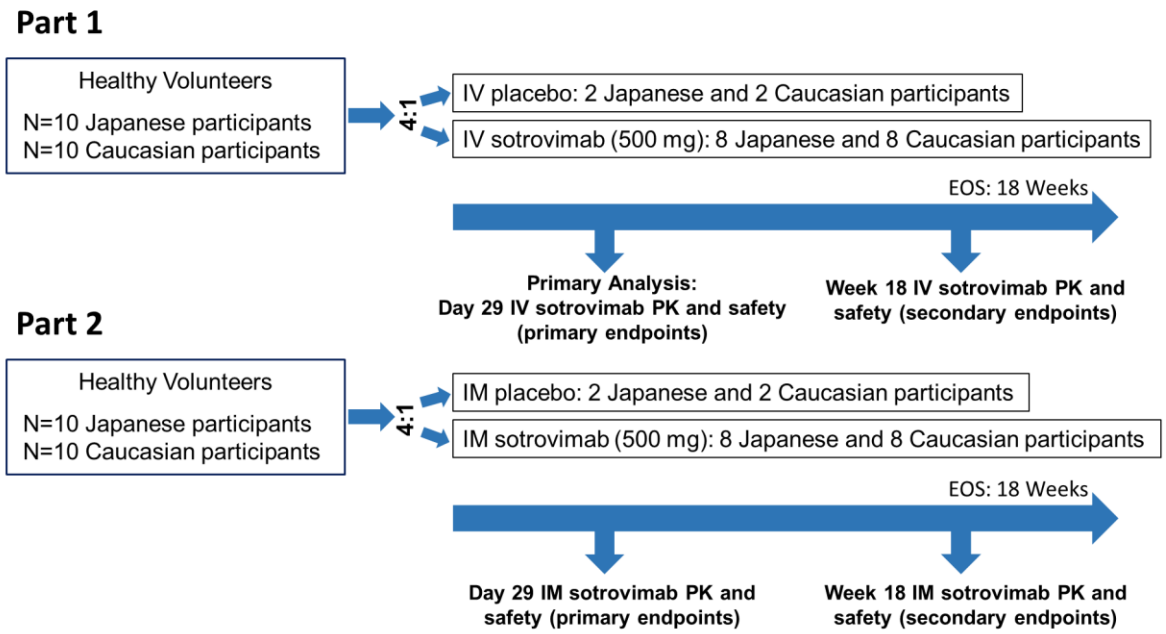
Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

This study will occur in two parts (Part 1 and Part 2). For both parts, Screening assessments will be performed within 28 days before administration of study intervention. After completion of Screening and Baseline assessments, eligible participants in Part 1 will be randomized 4:1 to receive a single-dose of IV sotrovimab (500 mg) or volume-matched placebo, while participants in Part 2 will be randomized 4:1 to receive a single-dose of IM sotrovimab (500 mg) or volume-matched placebo. Administration of study intervention will occur on Day 1. Participants will remain in the clinical research unit from admission on Day -1 through the completion of all Day 3 study procedures. Upon completion of this in-unit observation period, participants may be discharged as deemed clinically appropriate by the investigator. The follow-up period is for 18 weeks after dosing.

Data Monitoring/ Other Committee: No

1.2. Schema


Part 1
Healthy Volunteers
N=10 Japanese participants
N=10 Caucasian participants
4:1
IV placebo: 2 Japanese and 2 Caucasian participants
IV sotrovimab (500 mg): 8 Japanese and 8 Caucasian participants
EOS: 18 Weeks
Primary Analysis:
Day 29 IV sotrovimab PK and safety
(primary endpoints)
Week 18 IV sotrovimab PK and
safety (secondary endpoints)
Part 2
Healthy Volunteers
N=10 Japanese participants
N=10 Caucasian participants
4:1
IM placebo: 2 Japanese and 2 Caucasian participants
IM sotrovimab (500 mg): 8 Japanese and 8 Caucasian participants
EOS: 18 Weeks
Day 29 IM sotrovimab PK and
safety (primary endpoints)
Week 18 IM sotrovimab PK and
safety (secondary endpoints)

1.3. Schedule of Activities (SoA)

	Study Visit Day ± Visit Window	Screening[1] (up to D -28)	Day -1	W1 Day 1	W1 Day 2	W1 Day 3	W2 Day 8	W3 Day 15 ± 1d	W4 Day 29 ± 2d	W6 Day 43 ± 3d	W8 Day 57 ± 4d	W12 Day 85 ± 7d	W18 Day 127 ± 7d
	Admission to unit		X										
	Discharge from unit					X							
Screening	Informed consent	X											
Screening	Demographics	X											
Screening	Medical history (incl. medication/drug/alcohol/ tobacco use, allergies, illnesses, and SARS-CoV-2 infection/therapy/vaccination)	X	X[2]										
	Randomization			X									
	Study intervention administration			X									
Assessments	Full physical examination	X[3]		X		X							
Assessments	Vital Signs (BP, PR, RR, temperature, SpO_2)[4]	X		X[4]	X	X	X	X	X	X	X	X	X
Assessments	Local injection site tolerability assessment (intramuscular injections only)			X[5]	X[5]	X[5]							
Assessments	12-lead ECG[6]	X[6]		X[6]			X	X	X		X		X
Sample collection	Lab assessments (hematology, clinical chemistry, coagulation)	X		X[7]	X		X		X	X	X	X	X
Sample collection	Urinalysis and urine albumin to creatinine ratio	X		X[8]			X	X	X		X		X
Sample collection	Urine drug/alcohol screening	X	X										
Sample collection	HIV, Hepatitis B and C screening	X											
Sample collection	SARS-CoV-2 molecular test	X	X										
Sample collection	Pregnancy test[9]	X	X										X
Sample collection	Blood sample for PK analysis[10]			X[10]	X	X	X	X	X	X	X	X	X
Sample collection	Blood sample for immunogenicity testing (anti-drug antibody and drug-neutralizing antibody)			X[8]					X			X	X
	AE review			<========== X ==========>									
	SAE review	X[11]	X[11]	<========== X ==========>									
	AESI and concomitant medication review			<========== X ==========>									

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

NOTE: Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, 12-lead ECG, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. The actual time of assessment or procedure must be reported in the eCRF.

1. All screening procedures must be completed within 28 days prior to dosing.
2. Provide details of any changes to medical history since Screening.
3. Including height and weight.
4. Record Day 1 vital signs within 1 hour prior to dosing (IV and IM), at approximately 15 minutes after the infusion is started (IV only), and at the end of infusion (IV only) or immediately after injections (IM only). Vital signs will be monitored at approximately 30 minutes, 1 hour, and 2 hours after infusion or injection (IV and IM). Vital signs on other days should be performed once at any time of the day.
5. Local injection site tolerability assessment on Day 1 at approximately 1 hour post-dose and on Day 2 and Day 3. All ISRs need to be followed by the PI to resolution.
6. Triplicate 12-lead ECGs will be collected at Screening. All other timepoints are single 12-lead ECGs (unless an abnormality is detected post-baseline, in which case triplicate ECGs are required). On Day 1 ECGs will be performed at the following timepoints: prior to administration of study intervention (IV and IM), end of infusion (IV only), and at 1 hour and 2 hours after the end of IV infusion or first IM injection. On other days, ECGs will be performed once and time-matched to the PK sample collection.
7. Day 1 lab assessments should be collected pre-dose. Hematology assessments are performed only on Day 1.
8. On Day 1, sample collection will occur pre-dose.
9. Urine or serum pregnancy test, as per local guidelines. See Section 8.3.5.
10. Day 1 sample collection will occur pre-dose (IV and IM), at end of infusion (IV infusion only), and at 1, 2, 6, and 8, 24 (Day 2), and 48 (Day 3) hours after the end of infusion or first IM injection. On other days, samples will be collected once at any time of the day.
11. At screening and on Day -1, only SAEs related to study participation or a GSK product will be reported.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; GSK = GlaxoSmithKline; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EW = early withdrawal; HIV = human immunodeficiency virus; IM = intramuscular; ISRs = injection site reactions; IV = intravenous; PI = Principal investigator; PK = pharmacokinetic; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SpO_2 = oxygen saturation; PK = pharmacokinetics; PR = pulse rate; RR = respiratory rate

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak serum concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor/designee and site study files but will not constitute a protocol amendment.
- The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

Sotrovimab is being developed for treatment as well as for prophylaxis of Coronavirus disease 2019 (COVID-19). Sotrovimab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) derived from the parental mAb S309, a mAb directed against the spike protein of severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) that potently cross-neutralizes SARS-CoV-2, the causative agent of COVID-19 [Pinto, 2020]. The Fc domain of sotrovimab includes the 2 amino acid "LS" modification that extends antibody half-life and is also expected to enhance distribution to the respiratory mucosa [Ko 2014; Zalevsky, 2010; Gaudinski, 2018]. Previous clinical experience has been gained in ongoing studies of sotrovimab as a treatment for participants with mild to moderate COVID-19 (COMET-ICE [NCT04545060], BLAZE-4 [NCT04634409], COMET-PEAK [NCT04779879], and COMET-TAIL [VIR-7831-5008; GSK Study 217114]) and in hospitalized participants with COVID-19 (ACTIV-3-TICO [NCT04501978]).

This study is the first study in healthy Caucasian and Japanese participants. The purpose of this study is to evaluate the safety, tolerability, and PK of a single fixed dose of sotrovimab administered intravenously or via IM injection in Japanese and Caucasian healthy volunteers. These routes of administration were selected because of demonstrated efficacy of the IV route in early treatment of mild-to-moderate COVID-19 at high risk for progression, and to treat patients who lack access to IV infusion centers with IM injections; these are also the intended routes of administration for registration. The data from this study will be used to supplement data available from other clinical trials that were conducted in non-Japanese participants, will offer an opportunity for direct comparison of healthy Japanese to healthy Caucasian participants, and will support dose selection in Japan.

As of 31 MAR 2021, approximately 1350 participants have been randomized to either sotrovimab (500 mg IV dose) or placebo in two clinical studies: 1057 participants in a study evaluating sotrovimab for the treatment of non-hospitalized individuals with mild to moderate COVID-19 (COMET-ICE) and 300 participants in a study that evaluated sotrovimab for the treatment of individuals hospitalized with COVID-19 (ACTIV-3-TICO).

COMET-ICE was followed by an Independent Data Monitoring Committee (IDMC), whose most recent meeting was on 10 MAR 2021 for review of a planned interim analysis, which included 583 participants. There was an 85% reduction in the rate of hospitalization or death in the sotrovimab arm versus the placebo arm (p=0.002), which was the primary endpoint. The IDMC recommended that the study should halt enrollment on the basis of overwhelming efficacy [Vir Biotechnology, Inc., 2021].

ACTIV-3-TICO was followed by a Data and Safety Monitoring Board (DSMB) who met on 25 JAN 2021 to evaluate data from 148 participants who had been randomized to sotrovimab or shared placebo. One potentially life-threatening allergic reaction (anaphylaxis) was reported during infusion in ACTIV-3-TICO in a participant that

received sotrovimab. The time to onset was 21 minutes after the start of infusion and the event was considered related to study treatment. The participant was treated for the allergic reaction and recovered. The DSMB recommended the sotrovimab sub-study should continue as planned.

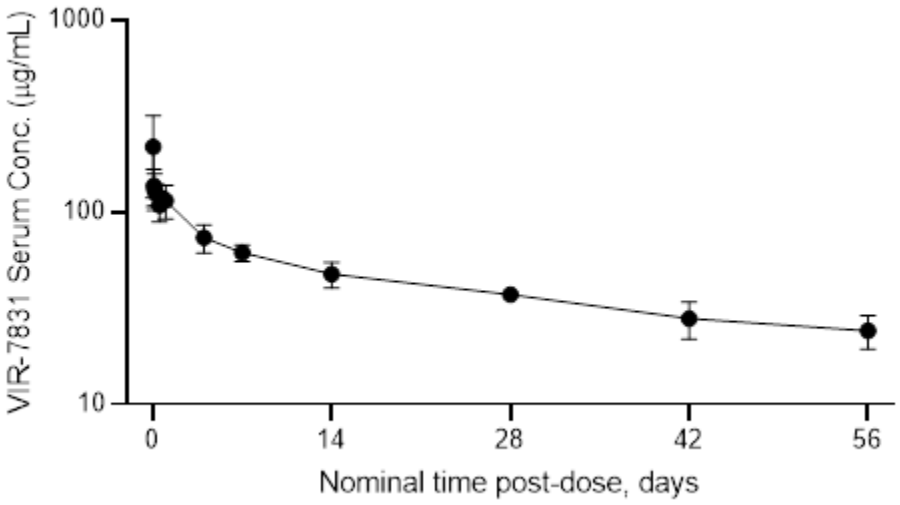
Most recently, the DSMB met on 01 MAR 2021 for a pre-planned safety and efficacy data review. While sotrovimab met initial pre-specified criteria to continue to the next phase of the ACTIV-3-TICO trial and there were no reported safety signals, sensitivity analyses of the available data raised concerns about the magnitude of potential benefit. The DSMB therefore recommended that the trial be closed to future enrollment [GlaxoSmithKline plc, 2021].

Sotrovimab administered by IV infusion is also being evaluated in the BLAZE-4 study, a clinical trial with multiple arms evaluating anti-SARS-CoV-2 mAbs from Eli Lilly and Company. One arm compared the combination of bamlanivimab with sotrovimab to placebo (randomized 1:1) for the treatment of mild to moderate COVID-19. Enrollment for this arm concluded at approximately 200 participants on 05 FEB 2021, with no new safety concerns for sotrovimab identified as of 17 MAR 2021. The BLAZE-4 study met the primary endpoint, with a 70% ($p<0.001$) relative reduction in persistently high viral load (>5.27; cycle threshold value <27.5) at Day 7 compared with placebo for bamlanivimab 700 mg co-administered with sotrovimab 500 mg. Co-administration of bamlanivimab and sotrovimab also demonstrated a statistically significant reduction in the key virologic secondary endpoints of mean change from baseline for SARS-CoV-2 viral load to Days 3, 5, and 7 compared with placebo [Eli Lilly and Company, 2021].

Sotrovimab administered intravenously (500 mg) or via IM injection (250 mg and 500 mg) is also currently being evaluated for the treatment of mild-to-moderate COVID-19 (COMET-PEAK) and in a study evaluating sotrovimab for the treatment of mild-to-moderate COVID-19 in non-hospitalized participants at high risk for disease progression (COMET-TAIL). As of 13 MAY 2021, safety data from approximately 30 participants who received 500 mg IV sotrovimab in Study Part A and from 66 participants who received 500 mg IV or IM sotrovimab in Study Part B of COMET-PEAK has been reviewed and no new safety concerns have been identified. Studies to evaluate IM injection (500 mg) of sotrovimab as a prophylaxis in immunocompromised participants and in persons living with HIV are also planned.

Partial blinded serum PK through Day 57 from the Lead-in phase of COMET-ICE is available to date. PK sampling will continue for 6 months for all participants in COMET-ICE. The preliminary pharmacokinetic (PK) profile and PK parameters for sotrovimab, based on nominal times are presented in Figure 1 and Table 1, respectively. The mean maximum concentration (C_{max}) of 500 mg sotrovimab was 219 µg/mL following a 1 hour IV infusion. The mean serum level on Day 29 is 37.2 µg/mL. Based on the partial data available to date, >20% of the area under curve (AUC) is being extrapolated and the observation range for the apparent terminal elimination rate constant (λ_z) spans <2 half-lives in all except one subject, so summary statistics for clearance (CL), apparent volume of distribution (V), terminal elimination half-life ($t_{1/2}$), and area under the serum concentration-time curve extrapolated to infinite time (AUC_{inf}) will be reported once sufficient data are available.

Figure 1 Preliminary Mean Concentration vs Time Profile of Sotrovimab in Serum: COMET-ICE Intensive Lead-in Pharmacokinetics



Note: Concentrations are displayed as mean ± standard deviation.

Table 1 Preliminary Sotrovimab Pharmacokinetic Parameters Following a Single 500 mg Intravenous Dose

Parameter	Dose 500 mg (N=9[a])
C_{max}, µg/mL	219 (45.5)
T_{max}, hour	1.0 (1.0, 1.0)
C_{last}, µg/mL	24.1 (19.7)
T_{last}, day	56.0 (56.0, 56.0)
C_{D29}, µg/mL	37.2 (7.6)
AUC_{D1-29}, day*µg/mL	1550 (10.1)
AUC_{last}, day*µg/mL	2350 (9.64)
$\%AUC_{exp}$, %	39.1 (29.5)
AUC_{inf}, day*µg/mL	TBD[b]
CL (mL/day)	TBD[b]
V_z, L	TBD[b]
$t_{1/2}$, day	TBD[b]

Abbreviations: AUC_{D1-29} = Area under the serum concentration-time curve, from Day 1 to Day 29; AUC_{last} = area under the curve from the time of dosing to the time of the last measurable (positive) concentration; AUC_{inf} = area under the serum concentration-time curve extrapolated to infinite time; $\%AUC_{exp}$ = The extrapolated portion of AUC_{inf}; C_{D29} = observed concentration on Day 29; C_{last} = observed concentration corresponding to T_{last}; C_{max} = maximum observed concentration; CL = clearance; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to reach C_{max}; TBD = to be determined; V_z = apparent volume of distribution during the elimination.

Parameters are reported as mean (percent coefficient of variation [%CV]) except for T_{max}, T_{last} and $t_{1/2}$, which are presented as median (Q1,Q3).

a. N=9 for C_{max}, T_{max}, C_{last}, $T_{last;}$ C_{D29}, N=8 for AUC_{D1-29}, AUC_{last}, $\%AUC_{exp}$.
b. Final summary statistics for AUC_{inf}, as well as CL, V, and $t_{1/2}$ will be reported when sufficient data are available so that ≤20% of the AUC_{inf} is extrapolated observation range for λ_z spans >2 half-lives.

2.2. Background

A novel beta-coronavirus causing severe pneumonia was first reported in December 2019 in Wuhan, China. Since that time, SARS-CoV-2 has spread throughout the world. As of 04 MAY 2021, there have been approximately 153 million confirmed cases and >3.2 million deaths globally with approximately 32 million cases and 577,584 deaths in the United States (US). In Japan, 613,819 cases and 10,441 deaths have been reported as of 04 MAY 2021 [Johns Hopkins COVID Dashboard, 2021].

Monoclonal antibodies directed against SARS-CoV-2 have the potential to be used for both the prevention and treatment of COVID-19 [Marovich, 2020]. Indeed, given developmental consideration [Kelley, 2020], mAbs could serve as an important bridge until vaccines are widely available. Specifically, neutralizing mAbs, given as early treatment in outpatients with mild to moderate COVID-19 disease could prevent need for hospitalization due to disease progression in patients at risk for complications such as respiratory compromise, respiratory failure, or other organ failure. Additionally, an efficacious neutralizing mAb given early in the disease course could ameliorate the severity and duration of COVID-19 and potentially reduce transmission. Given data demonstrating that viral loads are highest early in the course of disease [Wölfel, 2020; Zheng, 2020], the non-hospitalized patient population at high risk for disease progression may particularly benefit from early intervention with a mAb.

There are limited specific treatment options for patients with COVID-19, particularly for the outpatient population where the mainstay of treatment is monitoring and supportive care. In the US, an Emergency Use Authorization (EUA) was granted on 21 NOV 2020 for casirivimab and imdevimab (to be administered together), and on 09 FEB 2021 for bamlanivimab and etesevimab (to be administered together) for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization. Early reports from studies of mAbs in non-hospitalized patients with COVID-19 at high risk of progression to severe disease, as well as the recent EUAs for bamlanivimab/etesevimab and casirivimab/imdevimab, support the utility of mAbs in the treatment of COVID-19 in outpatients [Chen, 2021; Eli Lilly and Company, 2021; FDA, 2020; FDA, 2021].

Given that these mAbs are currently indicated for IV administration, a mAb that can be administered via IM injection would be of particular benefit in the outpatient setting where there are significant logistical challenges to IV administration. For example, most clinics require a dedicated infusion center with appropriate infection prevention and control measures to administer these mAbs to patients with early SARS-CoV-2 infection, as well as targeted allocation of resources and personnel for the close monitoring that is required during and post-infusion. A mAb that can be administered via IM injection could be provided in a substantially greater number of outpatient clinics that are currently not equipped for administration and monitoring of IV infusions, as well as possibly in the home care setting. Administration by an IM route also enables the potential to treat patients at high risk for poor outcomes in geographic areas where medical infrastructure is weak and the capacity to administer IV infusion is inadequate, including rural and underdeveloped regions.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: sotrovimab		
Infusion-related reactions (IRRs) including serious hypersensitivity reactions (HSR)	While sotrovimab is a human Immunoglobulin G1 (IgG1) mAb, IRRs are a potential general risk associated with the mAb class of therapeutics.	**Participant selection:** Participants will be excluded if they have a history of hypersensitivity to other mAbs or any of the excipients present in the investigational product. **Monitoring**: • Guidelines for monitoring relevant AEs encompassing hypersensitivity, angioedema and anaphylaxis as well as for the management of acute anaphylactic shock and minor allergic episodes will be in place at investigational sites. • Infusion time can be extended at the discretion of the Investigator or Sponsor based on local infusion-related symptoms or other safety findings. • Vital signs will be monitored approximately 15 minutes into the infusion and at the end of infusion. Vital signs will also be monitored at 30 minutes, 1 hour, and 2 hours in the post-infusion period. • Infusion-related reactions are categorized as AESI. **Mitigation**: • General guidance on management of HSRs is provided in Section 8.4.7.1 and such reactions will be managed appropriately per

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		local guidelines/medical judgment. Pre-medications will be permitted at the investigator's discretion and will be appropriately documented. • Investigators will be instructed to discontinue IV infusions for participants who develop Grade 3 or higher infusion reactions using the Division of Acquired Immune-deficiency Syndrome (DAIDS) *Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.1 (July 2017) Adverse Event grading (Section 10.3.3). • 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 of infusion, at the investigator's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids). • IV infusion will be administered in the clinic with staff trained in emergency care and resuscitation procedures and emergency care kit on hand during the infusion and post therapy observation periods.
Injection Site Reaction (ISR)	Sotrovimab will be administered via IM injection. A similar human IgG1 mAb specific to influenza A (VIR-2482) has been studied in a recent Phase I trial. Intramuscular injection of this IgG1 mAb, including at similar volumes as planned for the current study, was well-tolerated with minimal injection site reactions [Sager, 2020]. Specifically, dosing was well tolerated, with 6/100	Injection site reactions will be monitored very closely for 1 hour after injection and on Day 2 and Day 3 for all participants. Monitoring will also be performed for systemic symptoms post-dosing (e.g., fever, chills, malaise).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	participants experiencing mild injection site reactions that generally resolved within 48 hours. Through 12 weeks post-dosing, the majority (124/126) of AEs were mild to moderate in nature, no SAEs were reported, and no participants discontinued due to an AE.	
Immunogenicity	While sotrovimab is a human IgG1 mAb, the development of anti-drug antibodies (ADAs) that have the potential to impact safety and/or efficacy are a potential general risk associated with the mAb class of therapeutics. Drug-neutralizing antibodies, a subset of ADAs, have the potential to bind the drug and render it ineffective.	**Monitoring:** This study will include participant follow-up for a period of 18 weeks to assess for the potential of immunogenicity (measurement of ADA and drug-neutralization antibodies) as well as whether ADA and drug neutralizing antibodies are potentially causally associated with specific safety concerns.
Antibody-dependent enhancement (ADE) due to sub-neutralizing levels of sotrovimab enhancing fusion or leading to Fc Gamma Receptor (FcγR)-mediated increased viral uptake and replication with virus production	This is a concern related to the potential for participants with sub-neutralizing mAb levels to experience a higher incidence of re-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 re-infection with a different serotype can, in a minority of patients, run a more severe course in the setting of limited antibodies generated by prior infection. The potential for enhanced disease in this setting is due to increased uptake of virus by FcγR-expressing cells, such as macrophages, and increased viral replication in these cells. Recent data shows that SARS-CoV-2 does not replicate efficiently in macrophages [Hui, 2020], suggesting minimal to no risk of ADE via this mechanism.	**Monitoring:** This study will include participant follow-up for a period of 18 weeks to assess for the potential of enhanced disease in the context of waning sotrovimab levels.

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 endothelial, renal or cardiovascular (CV) 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 anti-viral 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 5000 COVID-19 patients treated with convalescent plasma, although not placebo controlled, is suggestive that even polyclonal mixtures of neutralizing and non-neutralizing antibodies can be safely administered [Joyner, 2020].	**Monitoring:** • Additional monitoring in the event a participant develops signs or symptoms of cardiac complications (See Section 8.3.3.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Sotrovimab shows potent binding as well as neutralization of pseudovirus and live virus *in vitro*, thus this risk is deemed to be low. Sotrovimab Clinical Experience: As of 31 MAR 2021, approximately 1350 participants have been randomized to either sotrovimab (500 mg IV dose) or placebo in two clinical studies: 1057 participants in a study evaluating sotrovimab for the treatment of non-hospitalized individuals with mild to moderate COVID-19 (COMET-ICE) and 300 participants in a study that evaluated sotrovimab for the treatment of individuals hospitalized with COVID-19 (ACTIV-3-TICO). Sotrovimab administered by IV infusion is also being evaluated in the BLAZE-4 study, with enrollment concluding at approximately 200 participants in the arm comparing the combination of bamlanivimab with sotrovimab to placebo. As of 13 May 2021 approximately 96 participants have been enrolled in COMET-PEAK. Further details regarding review of safety data from these trials are provided in Section 2.1.	

2.3.2. Benefit Assessment

Participation in this study will provide valuable scientific knowledge about sotrovimab in the Japanese population. Sotrovimab is being developed for the treatment of COVID-19.

Interim analysis of data from 583 participants in COMET-ICE, a study evaluating sotrovimab for the treatment of non-hospitalized individuals with mild to moderate COVID-19, was reviewed on 10 MAR 2021. There was an 85% reduction in the rate of hospitalization or death in the sotrovimab arm versus the placebo arm (p=0.002), which was the primary endpoint. The IDMC recommended that the study halt enrollment on the basis of overwhelming efficacy [Vir Biotechnology, Inc., 2021].

Although studies are planned or underway to evaluate sotrovimab for COVID-19 prophylaxis in immunocompromised individuals, no studies to assess direct benefit to healthy volunteers for prophylaxis have been completed; therefore, no direct benefit for healthy participants in this study is currently known. However, participants may benefit in the knowledge that they are contributing to the process of developing new therapies in an area of unmet need. Participants may also benefit from the thorough medical assessments they receive during the course of the study.

Mitigation strategies, including physical examinations, laboratory evaluations, and electrocardiograms, as outlined in the SoA (Section 1.3), are included to limit the risk to participants.

2.3.3. Overall Benefit: Risk Conclusion

The overall benefit-risk assessment takes into account the potential benefit of sotrovimab treatment for COVID-19 in the Caucasian and Japanese populations.

No clinical studies of sotrovimab have been completed to date. There is prior clinical experience with sotrovimab in the setting of the early treatment of COVID-19 (COMET-ICE, COMET_PEAK, and BLAZE-4) and hospitalized treatment in ACTIV-3-TICO. In the COMET-ICE study, there have been no significant safety concerns identified at the IDMC reviews conducted to date. As of 17 MAR 2021, there have been no safety concerns identified in the BLAZE-4 study. In the ACTIV-3-TICO study, one case among 360 participants who received sotrovimab experienced anaphylaxis during infusion of the drug, which resolved with treatment. As of 13 MAY 2021, safety data from approximately 96 participants who received 500 mg IV or IM sotrovimab in COMET-PEAK has been reviewed and no new safety concerns have been identified.

Sotrovimab has the potential to be an effective therapeutic in mild to moderately ill patients with COVID-19. This benefit has been demonstrated in the interim analysis of the COMET-ICE study, a study of participants with mild to moderate COVID-19 at high risk of disease progression [Vir Biotechnology, Inc., 2021]. Human-derived mAbs with similar Fc modifications as sotrovimab have a well-established safety profile [Gaudinski, 2018]. Considering the measures taken to minimize risk to participants in this study, data supporting the safety of sotrovimab, the limited disease-directed therapeutic options for COVID-19, and the existing knowledge gap in healthy participants in general and

ethnically Japanese participants in particular, the overall benefit-risk assessment of this study is considered favorable based on the available data.

3. OBJECTIVES AND ENDPOINTS

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

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

Objectives	Endpoints
Exploratory	
Immunogenicity (Part 1) To assess the immunogenicity of IV sotrovimab in healthy Japanese and Caucasian participants	Incidence and titers (if applicable) of serum ADAs and drug-neutralizing antibodies to sotrovimab through Week 18.
Immunogenicity (Part 2) To assess the immunogenicity of IM sotrovimab in healthy Japanese and Caucasian participants	Incidence and titers (if applicable) of serum ADAs and drug-neutralizing antibodies to sotrovimab through Week 18.

[a] Baseline is defined as assessments performed following admission to unit on Day -1 and before dosing on Day 1.

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, multi-center, placebo-controlled, single-blind, single-dose, parallel group Phase I trial to assess the PK of IV and IM sotrovimab in healthy Japanese and Caucasian participants.

This study will occur in two parts (Part 1 and Part 2). For both parts, screening assessments will be performed within 28 days before administration of study intervention. Administration of study intervention will occur on Day 1. Participants will remain in the clinical research unit from admission on Day -1 through the completion of all Day 3 study procedures. Upon completion of this in-unit observation period, participants may be discharged as deemed clinically appropriate by the investigator. Participants will return for outpatient visits throughout the 18 weeks following administration of study intervention, as shown in the SoA (Section 1.3). Participants can be screened up to 28 days before dosing, leading to a maximum study duration of 22 weeks.

Part 1:

Healthy Japanese and Caucasian participants will be randomized in a 4:1 ratio to receive a single, 500 mg IV infusion of sotrovimab or volume-matched saline placebo. A maximum of 24 participants will be randomized to Part 1 to achieve 20 evaluable participants in Part 1. The Part 1 cohort will enroll approximately 8 Japanese and 8 Caucasian participants to the IV sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm. Eligible participants will be treated with a single IV dose of sotrovimab or placebo on Day 1. Participants will be blinded to study intervention. Safety, tolerability, immunogenicity, and PK of IV sotrovimab will be evaluated.

Part 2:

Part 2 will begin after enrollment for Part 1 is completed. Healthy Japanese and Caucasian participants will be randomized in a 4:1 ratio to receive a single 500 mg IM dose of sotrovimab (administered as two 4 mL injections, one in each dorsogluteal muscle) or volume-matched saline placebo. A maximum of 24 participants will be randomized to Part 2 to achieve 20 evaluable participants in Part 2. The Part 2 cohort will enroll approximately 8 Japanese and 8 Caucasian participants to the IM sotrovimab arm and 2 Japanese and 2 Caucasian participants to the placebo arm. Eligible participants will be treated with a single IM dose of sotrovimab or placebo on Day 1. Participants will be blinded to study intervention. Safety, tolerability, immunogenicity, and PK of IM sotrovimab will be evaluated.

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

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

4.2. Scientific Rationale for Study Design

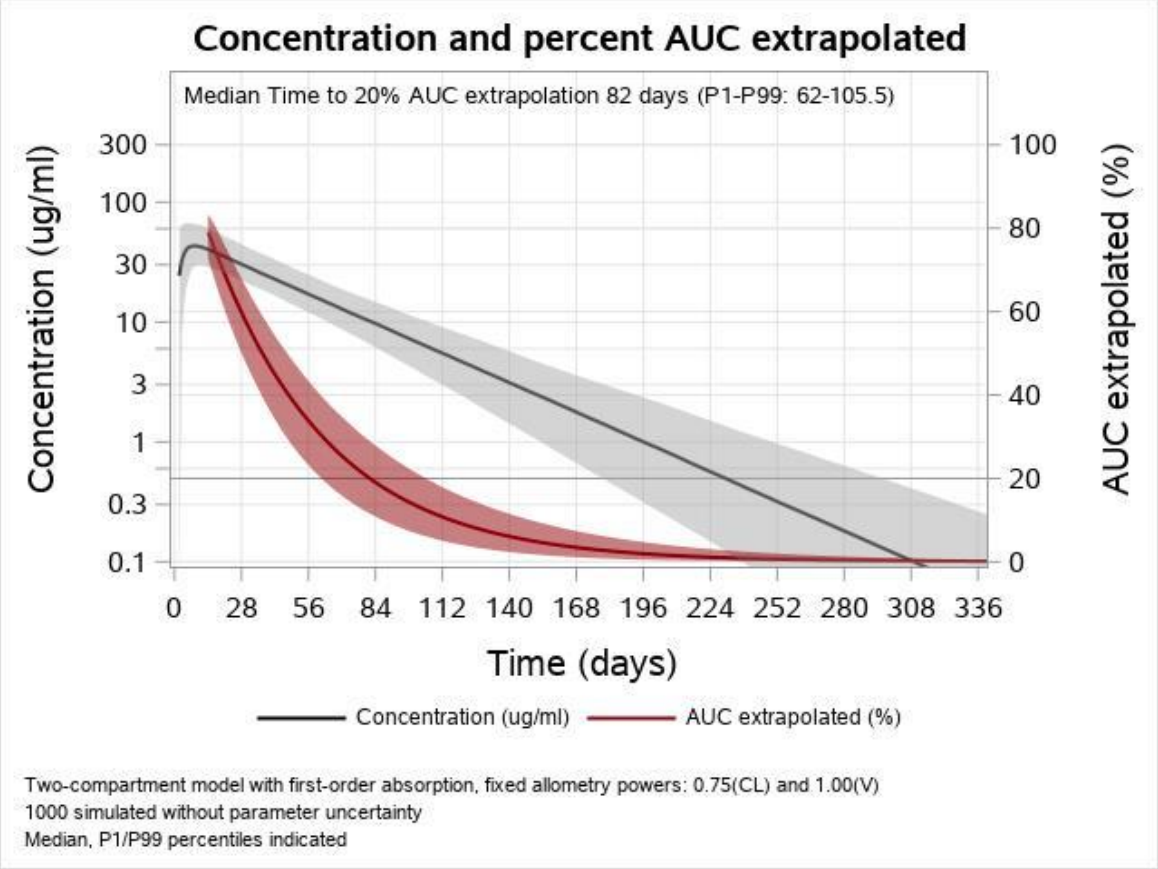
This study includes a placebo arm to allow for a valid evaluation of AEs attributable to sotrovimab versus those independent of sotrovimab (such as regression towards the mean). A single-blind design is a common methodology for randomized, controlled PK bridging studies to minimize bias arising from study participants based on their knowledge of receipt of study drug. To date, SARS-CoV-2-directed mAbs as a class have had favorable safety profiles [Regeneron Pharmaceuticals, Inc., 2020; Eli Lilly and Company, 2020]. Therefore, the marginal benefit when comparing single-blind to double-blind design is minimal; however, single-blinding will minimize bias originating from participants that may occur during study assessments, including during evaluation of AEs and disease-related safety outcomes.

Body weight is the principal determinant of mAb exposure. Body weight is expected to be the primary determinant of differences in the drug PK; therefore, all analyses will be adjusted for body weight. A difference in the average body weight of Japanese and Caucasian participants necessitates a direct comparison of the PK and safety profiles in these two populations. Ethnically Japanese patients with mild-to-moderate COVID-19 were not represented in the safety and efficacy studies included in COMET-ICE. Therefore, this study represents the first evaluation of sotrovimab in the Japanese population. Additionally, this study is the first use of sotrovimab in healthy volunteers; therefore, data previously obtained for Caucasian patients with COVID-19 in COMET-ICE cannot be used for direct comparison to healthy Japanese participants.

The number of participants randomized to each arm will provide acceptable precision for PK estimation. Due to the extended half-life of sotrovimab, 18 weeks is the minimum

duration predicted to have the extrapolated portion of the AUC being less than 20% (Figure 2).

Figure 2 Concentration and Percent Area Under the Curve (AUC) Extrapolated vs Time



4.3. Justification for Dose

The 500 mg IV dose of sotrovimab to be evaluated in this study was selected based on extensive nonclinical data and expected human PK extrapolated from cynomolgus monkeys. This 500 mg IV dose is currently being evaluated in ongoing clinical trials COMET-ICE, ACTIV-3-TICO, and BLAZE-4, with approximately 1550 participants randomized to either sotrovimab (500 mg dose) or placebo to date.

A 500 mg IM dose was selected for Part 2 of this study based on *in vitro* neutralization data, *in vitro* resistance data, and simulated IM PK based on preliminary IV PK from the 500 mg dose that is being evaluated in ongoing clinical studies (COMET-ICE, ACTIV-3-TICO, BLAZE-4, COMET-PEAK, and COMET-TAIL). The 500 mg IV and 500 mg IM doses are currently being evaluated in ongoing clinical trial COMET-PEAK, with approximately 96 participants receiving 500 mg IV or 500 mg IM sotrovimab as of 13 MAY 2021, and these doses will also be evaluated in COMET-TAIL.

Sotrovimab neutralizes SARS-CoV-2 live virus with an average 90% effective concentration (EC_{90}) value of 186.3 ng/mL (range: 125.8–329.5 ng/mL) (PC-7831-0105).

In resistance analyses, no viral breakthrough was observed through 10 passages at fixed concentrations of antibody, indicating the potential for sotrovimab to have a high barrier to resistance (PC-7831-0109). Using an increasing concentration selection method to force resistance emergence, E340A was identified as a monoclonal antibody-resistant mutant (MARM) conferring a >100-fold reduction in susceptibility to sotrovimab. Notably, E340 is 99.9% conserved among available SARS-CoV-2 sequences. Due to the binary nature of the resistance selection results, a specific inhibitory quotient was not informed by the resistance profiling.

Based on preliminary IV PK data from the Lead-in phase of an ongoing clinical study evaluating sotrovimab in the early treatment of COVID-19 (COMET-ICE; NCT04545060), the mean Day 29 serum concentration of sotrovimab following a single 500 mg IV dose is 37.2 µg/mL (N=9). Based on the PK data available to date, >20% of the AUC is being extrapolated so final CL, V, AUC and $t_{1/2}$ have not been determined; however, a preliminary estimate of the median half-life of sotrovimab is approximately 47 days.

A 500 mg IM dose was selected to ensure that sotrovimab concentrations in lung are maintained at or above levels anticipated to be neutralizing for the duration of the treatment window. Based on the EC_{90} (0.33 µg/mL) from the highest end of the EC_{90} range (PC-7831-0105), and accounting for the lung:serum ratio for immunoglobin G (IgG; assumed conservative value of 0.25; reported range 0.25 to 0.68 for whole lung and interstitial fluid, respectively [Baxter, 1994; Covell, 1986; Datta-Mannan, 2019; Lobo, 2004]); and assuming 70% bioavailability following IM administration, an IM dose of 500 mg is expected to maintain serum levels at or above 10x lung tissue adjusted EC_{90} through the Day 29 primary endpoint.

Prior clinical experience with a 500 mg IV dose of sotrovimab has been gained in the setting of the early treatment of COVID-19 (COMET-ICE, BLAZE-4, and COMET PEAK) and hospitalized treatment in ACTIV-3-TICO. In the COMET-ICE study, there have been no significant safety concerns identified at the IDMC reviews conducted to date. Furthermore, an interim analysis of data from 583 high-risk patients demonstrated an 85% (p=0.002) reduction in hospitalization or death in patients receiving sotrovimab compared to placebo [Vir Biotechnology, Inc., 2021]. In ACTIV-3-TICO, one case of anaphylaxis was reported during infusion of sotrovimab which resolved with treatment. In the BLAZE-4 study, there have been no safety concerns identified as of 17 MAR 2021. A Joint Safety Review Team (JSRT) met on 13 MAY 2021 to review data from participants enrolled in COMET-PEAK to date and no emerging safety issues were detected; the JSRT recommended a reduction in monitoring time for this study.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit for the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the respective part of the study to which he/she was enrolled (Part 1 or Part 2) through Week 18.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Participants who do not meet screening criteria may be rescreened, as described in Section 5.4.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age inclusive, at the time of signing the informed consent. Additionally, participants 55 years or older, at the time of signing informed consent will be permitted only if they have received all doses in a SARS-CoV-2 vaccine series.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Participants must be negative for COVID-19, determined by two consecutive negative results by any validated SARS-CoV-2 molecular test (e.g. reverse transcriptase polymerase chain reaction [RT-PCR] on any respiratory type) separated by >24 hours prior to unit admission. The first test may be carried out at any time during Screening, the second test will be at Day -1.
4. For Japanese participants, participant must meet all of the following: Japanese ancestry, defined as having been born in Japan, being descendants of four ethnic Japanese grandparents and two ethnic Japanese parents, holding a Japanese passport or identity papers, and being able to speak Japanese. Participants should have lived outside Japan for fewer than 10 years at the time of Screening.
5. For Caucasian participants, participant must meet all of the following: Caucasian ancestry, defined as Caucasian descent as evidenced by appearance and verbal confirmation of familial heritage (a participant has 2 Caucasian parents and 4 Caucasian grandparents).

Weight

6. Body weight considering body mass index (BMI) within the range of 18 to 29.9 kg/m^2 (inclusive).

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.

OR

b. Is a woman of child-bearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least 24 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) at Screening and on Day -1, before the first dose of study intervention. See Section 8.3.5 Pregnancy Testing.

– 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 8.3.5.
- 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.

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data.
2. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

3. Breast cancer within the past 10 years.
4. Abnormal blood pressure as defined as greater than 140 mm/Hg systolic, greater than 90 mm/Hg diastolic, or less than 90 mm/Hg systolic at Screening. Blood pressure at Screening is the average of 3 blood pressure readings taken using the methods described in Section 8.3.2.
5. Significant allergies to humanized monoclonal antibodies.
6. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
7. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
8. Total bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).
9. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

Prior/Concomitant Therapy

10. Use of any prescription medications within the 28 days prior to dosing or concomitantly, unless permitted in Section 6.8 or approved by the Investigator in conjunction with the GSK medical monitor.
11. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.
12. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.
13. Receipt of any vaccine within 48 hours prior to enrollment. Vaccination will not be allowed for 90 days after dosing.
14. Has received a SARS-CoV-2 vaccine but has not completed all doses in the series more than 28 days prior to Screening. SARS-CoV-2 vaccinations will not be allowed for 90 days after dosing.

Prior/Concurrent Clinical Study Experience

15. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56 day period.
16. Exposure to more than 4 new chemical entities (e.g., investigational pharmaceuticals) within 12 months prior to the first dosing day.
17. Current enrollment or past participation in this clinical study.
18. 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.

Diagnostic assessments

19. Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to first dose of study intervention.
20. Positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
21. Positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
22. Positive pre-study drug/alcohol screen.
23. Positive HIV antibody test.

Other Exclusions

24. History of regular alcohol consumption within 6 months prior to the study defined as:
    - An average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.
25. Regular use of known drugs of abuse.
26. Sensitivity to any of the study interventions, or components thereof, or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants should arrive fasted for the Screening Visit only and will be allowed to eat during the Screening Visit after blood draw for clinical chemistry has been completed.

5.3.2. Caffeine, Alcohol, and Recreational Drug Use

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 6 hours prior to the visits that include ECG assessments, and during those visits.
- Participants will abstain from alcohol for 24 hours prior to each visit to the clinic and during the in-patient period.
- Participants must have a negative drug test at screening and admission to the clinical unit and must abstain from recreational drug use from screening until after the final follow-up visit.

5.3.3. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.3.4. Other Restrictions

Participants cannot donate blood or blood products for 24 weeks after administration of study intervention.

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 SAEs.

If a participant fails any of the laboratory exclusion criteria, the test may be repeated once within the Screening period. If the participant fails the laboratory criteria for a second time, they will be considered a screen failure. Retesting within screening window of any blood sample withdrawn due to sample handling problems, breakage or sample integrity is not considered a rescreening.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 2 times. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

Details of study interventions for Part 1 are provided Table 2 in and details for Part 2 are provided in Table 3. An ingredient in the sotrovimab formulation that may cause hypersensitivity is the surfactant polysorbate-80. The sotrovimab formulation also contains sucrose, histidine and methionine.

For IM injections, the study intervention will be given as two 4 mL injections, one in each dorsogluteal muscle.

Table 2 Part 1 Study Interventions

Arm Name	**IV Sotrovimab**	**IV Placebo**
Intervention Name	VIR-7831	Placebo
Type	Biologic	Placebo to Biologic
Dose Formulation	Solution in single use vial (62.5 mg/mL)	Sterile 0.9% (w/v) sodium chloride solution
Unit Dose Strength(s)	500 mg/vial (500 mg/8 mL)	Not applicable
Dosage Level(s)	500 mg once diluted in saline to 5 mg/mL to 10 mg/mL. Volume range: 50 mL to 100 mL	Given in equal volume to VIR-7831 IV
Route of Administration	IV infusion	IV infusion
Duration of infusion	30 minutes	30 minutes
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	Sotrovimab will be provided centrally by the sponsor/designee	Saline for placebo will be provided by the site.
Packaging and Labeling	Sotrovimab study intervention will be provided in a single-use vial and labeled as required per country requirement.	Site to provide commercially available saline.
Current/Former Name(s) or Alias(es)	VIR-7831, GSK4182136, sotrovimab	Not applicable

Table 3 Part 2 Study Interventions

Arm Name	**IM Sotrovimab**	**IM Placebo**
Intervention Name	VIR-7831	Placebo
Type	Biologic	Placebo to Biologic

Arm Name	**IM Sotrovimab**	**IM Placebo**
Dose Formulation	Solution in single use vial (62.5 mg/mL)	Sterile 0.9% (w/v) sodium chloride solution
Unit Dose Strength(s)	500 mg/vial (500 mg/8 mL)	Not applicable
Dosage Level(s)	8 mL=500 mg once	8 mL=500 mg once
Route of Administration	IM injection	IM injection
Duration of infusion	Not applicable	Not applicable
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	Sotrovimab will be provided centrally by the sponsor/designee	Saline for placebo will be provided by the site.
Packaging and Labelling	Sotrovimab study intervention will be provided in a single-use vial and labeled as required per country requirement.	Site to provide commercially available saline.
Current/Former Name(s) or Alias(es)	VIR-7831, GSK4182136, sotrovimab	Not applicable

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.
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor, and/or Sponsor study contact.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a single-blind study. Only the participant will be blinded to the treatment. The investigator or treating physician, site staff, GSK, and the Sponsor will be unblinded.

The investigator should assure and maintain the blindness of information relating to the assigned investigational product to participants. The investigator or treating physician, site staff, GSK, and the Sponsor must not share any potentially unblinding investigational product information with the participants during the study conduct period, until formal unblinding has taken place.

All participants will be centrally randomized using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

In Part 1, participants will be randomized in a 4:1 ratio to receive an IV infusion of sotrovimab or volume-matched saline placebo. In Part 2, participants will be randomized in a 4:1 ratio to receive sotrovimab or volume-matched saline placebo via IM injection. Participants will be blinded to study intervention; however, site staff will not be blinded.

Monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

A participant may continue in the study if that participant's intervention assignment is unblinded.

GlaxoSmithKline's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention Compliance

Participants will be dosed at the site and they will receive study intervention (sotrovimab or volume-matched saline placebo) directly from the investigator or designee, under medical supervision. The date and start and stop times of the IV dose (Part 1) and the date and administration time of each IM injection (Part 2) 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 for this study. 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

There will not be continued access to study intervention after the end of the study.

6.7. Treatment of Overdose

For this study, any dose of sotrovimab greater than the protocol-defined dose and frequency (one-time dose) will be considered an overdose.

No specific treatment is recommended for an overdose. The treating physician may provide supportive measures depending on the symptoms.

In the event of an overdose, the treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the case report form (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:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Receipt of any vaccine is not permitted within 90 days after dosing. Receipt of any investigational (not authorized or approved) SARS-CoV-2 vaccine is not permitted during the study. Receipt of any authorized or approved SARS-CoV-2 vaccine is permitted following 90 days post-dosing. Participants should consult with the primary investigator and their primary care physician on local guidelines for vaccine administration and guidance on the risks associated with administration of a SARS-CoV-2 vaccine while on study.

Participants must abstain from taking prescription or non-prescription drugs for 28 days before the start of study intervention until completion of the Week 18 visit, unless, in the opinion of the investigator in consultation with the Medical Monitor, the medication will not interfere with the study. Medications that could potentially affect the renal system should be avoided, e.g., NSAIDs (non-steroidal anti-inflammatory drugs).

Over the counter medications for nutritional support such as vitamins, minerals, amino acids, and herbal or botanical supplements are permitted for use at any time during the study. Paracetamol/acetaminophen, at doses of ≤2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

All prior and concomitant medication should be captured in the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. For IV administration, a participant will be permanently discontinued from completion of drug infusion if they experience a Grade 3 or 4 IRR (for example, life-threatening, infusion-related reactions including severe allergic or HSRs or severe cytokine release syndrome).

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for follow-up assessments. Post-dose monitoring, assessments and procedures, per the SoA (Section 1.3), should be completed as planned.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. As this is a single-dose study, liver chemistry stopping criteria for a single participant are not applicable; however, further enrollment in this study may be stopped if liver chemistry tests during follow-up visits indicate abnormal liver function without an identifiable underlying etiology.

Refer to Section 10.5 for required Liver Safety Actions and Follow up Assessments. ALT ≥3 times the ULN needs to reported within 24 hours. If it is a possible Hy's Law case, report as an SAE. A possible Hy's Law case is defined as ALT ≥3xULN **and** total

bilirubin ≥2xULN (>35% direct) **or** INR>1.5 (INR value not applicable to participants on anticoagulants).

7.1.2. Temporary Discontinuation

For IV administration, 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 (e.g. antihistamines, IV fluids). If a participant experiences a Grade 1 IRR the infusion can continue with close follow-up at the Investigator's discretion.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, 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 discontinuing from the study, if possible, an early discontinuation visit (ED) should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor/designee may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- If participants permanently discontinue the study before Day 29, additional participants may be enrolled as replacements and assigned to the same cohort and treatment at the discretion of the Sponsor or designee in consultation with the investigator.

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.

- 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

- Study procedures and their timing are summarized in the SoA (Section 1.3). Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, 12-lead ECG, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. The actual time of assessment or procedure must be reported in the eCRF.
- Participants will remain in the clinical research unit from admission on Day -1 through the completion of all Day 3 study procedures. Upon completion of this in-unit observation period, participants may be discharged as deemed clinically appropriate by the investigator. Participants will return for outpatient visits throughout the 18 weeks following administration of study intervention, as shown in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- 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.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for Screening or Baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Typical blood volumes expected during the usual course of study participation will be approximately 150 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Screening Period

Informed consent must be obtained before conducting any study procedures. Screening will be performed no more than 28 days prior to randomization and include the assessments outlined in the SoA (Section 1.3).

8.1.1. Medical History

Relevant medical history within the last three years, as determined by the Investigator, should be reported. Details regarding history of medication, drug, alcohol, and tobacco use will be reported. Details regarding illnesses (including COVID-19) 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 as indicated in the SoA (Section 1.3).

8.1.2. SARS-CoV-2 Testing

Participants will be tested for SARS-CoV-2 as outlined in the SoA (Section 1.3). The following criteria must be met for a participant to be included in this study:

- Two consecutive negative results by any validated SARS-CoV-2 molecular tests (e.g., RT-PCR on any respiratory type) separated by >24 hours. The first test may be carried out at any time during Screening, the second test will be at Day -1.

8.2. Efficacy Assessments

Not applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

Physical examinations will be conducted as described in the SoA (Section 1.3).

- A full physical examination will include, at a minimum, assessments of the Skin, CV, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature (oral preferred), pulse rate, respiratory rate, SpO_2 and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed 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).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse (the first heart rate reading) and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

Part 1:

Day 1: Vital signs will be monitored within 1 hour prior to the infusion. Vital signs will be monitored at approximately 15 minutes into the infusion and at the end of infusion. Vital signs will also be monitored at approximately 30 minutes, 1 hour, and 2 hours after the end of infusion.

Vital signs on study visit days other than Day 1 will be collected once at any time of the day, as indicated in the SoA (Section 1.3).

Part 2:

Day 1: Vital signs will be monitored within 1 hour prior to IM injections. Vital signs will be monitored immediately after injections and at approximately 30 minutes, 1 hour, and 2 hours after injection.

Vital signs on study visit days other than Day 1 will be collected once at any time of the day, as indicated in the SoA (Section 1.3).

8.3.3. Electrocardiograms

ECGs will be obtained as described in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.

Electrocardiograms will be performed locally. Digital ECG waveforms will be archived centrally. Fridericia's correction formula will be used to determine the QTc. The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding on ECGs should be reported as an AE.

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

For triplicate 12-lead ECGs, each of the 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minutes) recording period.

If an ECG abnormality is detected post-Baseline, ECGs should be performed in triplicate.

8.3.3.1. Cardiac Monitoring

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

8.3.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency. Clinical laboratory tests will be performed by local laboratories.
- 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.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 weeks after the last dose of study intervention 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 any 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/designee notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- 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 or dose modification), then the results must be recorded.

8.3.5. 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, on Day -1, and at Week 18 or the Early Withdrawal Visit.
- 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.

8.3.6. Local Injection Site Tolerability

For IM injections in Part 2 of the study, a local injection site tolerability assessment will be performed per the Schedule of Activities (Section 1.3). Injection sites should be monitored for any adverse events. Refer to Section 8.4.2 for assessment of AE severity.

A local injection site tolerability assessment will be performed approximately 1 hour after injection and on Day 2 and Day 3 for all participants. Any ISRs will need to be followed by the principal investigator (PI) for resolution.

At the discretion of the investigator, unscheduled visits are permitted as needed for follow up of any unresolved local injection site tolerability symptoms. Management guidelines for these symptoms are provided in Section 10.6.

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

NOTE:GSK is acting on behalf of the Sponsor, Vir, for the purposes of global safety reporting for this study.

The definitions of AEs or SAEs can be found in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 all AEs considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

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

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

- All SAEs and AEs will be collected from the administration of study intervention until Week 18 (EOS) at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- 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 GSK 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 GSK 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 GSK.

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 (refer to Section 10.3.3).

8.4.3. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. 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 8.4.7), 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

- Prompt notification by the investigator to GSK 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.
- GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. GSK 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.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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 18 or the EW Visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate/child for 8 weeks after the birth and the information will be forwarded to the GSK.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the GSK as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant after administration of study intervention should not be withdrawn from the study, unless the participant chooses to be withdrawn.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest are defined in the study protocol as relevant known toxicities of other therapeutic mAbs or as a result of signals observed from previous studies in the nonclinical programs of sotrovimab that will be monitored by the sponsor or designee either during or at the end of the study (through Week 18). These will be updated during the course of the study based on accumulating safety data.

AESI include:

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

8.4.7.1. Infusion-Related Reactions and Serious Hypersensitivity

Guidelines for monitoring relevant AEs encompassing hypersensitivity, angioedema and anaphylaxis as well as for the management of acute anaphylactic shock and minor allergic episodes will be in place at investigational sites. Investigators will be provided with general guidance on management of serious HSRs and such reactions will be

managed appropriately per local guidelines/medical judgment. Pre-medications will be permitted at the investigator's discretion and will be appropriately documented.

8.4.7.2. Injection Site Reactions

Study participants should be monitored after administration of study intervention for signs or symptoms of any injection site reactions as described in the SoA (Section 1.3). Any events observed or reported should be noted utilizing the DAIDS criteria as described in Section 10.3.3.

8.4.7.3. Immunogenicity

Therapeutic proteins, including mAbs, have the potential to induce an unwanted immune response (immunogenicity) in humans. This reaction leads to production of ADAs which may inactivate the therapeutic effects of the treatment and, in rare cases, induce AEs. This study will include participant follow-up for a period of 18 weeks to assess for the development of ADA and drug-neutralizing antibodies and potential impacts on safety, PK, and/or efficacy.

8.4.7.4. Antibody-Dependent Enhancement

Antibody-Dependent Enhancement of disease theoretically can occur via one of three previously described mechanisms:

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

The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations [Arvin, 2020]. This study will recruit healthy volunteers without evidence of SARS-CoV-2 infection at the time of dosing with sotrovimab. Due to the long half-life of this antibody, it is possible for participants to become infected with SARS-CoV-2 as serum concentrations of sotrovimab wane during the course of the 18 week follow-up period. This study will assess for the potential of enhanced disease in the context of waning sotrovimab levels followed by infection or re-infection in participants who recovered from prior COVID-19. ADE may manifest as an increased incidence of severe disease in participants infected with SARS-CoV-2 for the first time or increased incidence or severity of re-infection in participants who recovered from prior 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. The third mechanism is highly unlikely to occur in this study in healthy participants who are not infected with SAR-CoV-2 at the time of dosing. In the very unlikely event that it could occur, this may manifest as increased severity or duration of illness in sotrovimab-treated participants compared to what would be clinically expected.

8.5. Pharmacokinetics

Blood samples for sotrovimab serum PK will be collected as detailed in the Schedule of Activities (Section 1.3).

- Serum concentration time data for sotrovimab will be analyzed by non-compartmental methods
- The actual collection date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of sotrovimab serum concentration may also be used to evaluate safety 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 sotrovimab, one sample of sufficient volume can be used.
- Instructions for the collection and handling of biological samples will be provided by the sponsor or designee.
- The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak serum concentrations) to ensure appropriate monitoring.

PK parameters will be computed using standard noncompartmental methods. Parameters may include, but are not be limited to, those shown in Table 4.

Table 4 PK Parameters

Objective	Parameters
Primary PK (through D29)	C_{max}, AUC_{D1-29}, T_{max}, C_{D29}
Secondary PK (through Week 18)	C_{max}, AUC_{inf}, AUC_{last}, T_{max}, T_{last}, $t_{1/2}$

As data permits other PK parameters in addition to the listed above may be calculated and will be listed and summarized using descriptive statistics. Definitions of PK parameters, methods for estimation and details of PK analyses for each study Part will be included in the analysis plan.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Antibodies to sotrovimab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). If a participant was discontinued early from study intervention or was withdrawn from the study, serum samples should also be

collected at the final visit. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to sotrovimab and the titer of confirmed positive samples will be reported. 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. 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 or designee to enable further analysis of immune responses to sotrovimab.

8.9. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

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

9.2. Sample Size Determination

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

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

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

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

9.3. Analysis Sets

The following analysis sets are defined for the purpose of analysis.

Participant Analysis Set	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who entered the study. Note: screen failures are excluded from the Enrolled analysis set as they did not enter the study.
Randomized	All participants who were randomly assigned to study intervention. Data will be reported according to the randomized intervention.
Safety	All randomized participants who were exposed to study intervention. Participants will be reported according to the intervention they actually received.
Pharmacokinetic	All participants in the Safety analysis set who had at least 1 non-missing PK assessment – i.e., PK sample collected and analysed. Note: Non-quantifiable [NQ] values will be considered as non-missing values. Participants will be reported according to the intervention they actually received.

9.4. Statistical Analyses

9.4.1. General Considerations

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary and key secondary endpoints.

9.4.2. Primary Endpoint(s)

For the analyses planned in the following sections, potential intercurrent events or events leading to missing data that will be considered are discontinuation or interruption of administration of study intervention and participant withdrawal from study or lost to follow-up.

9.4.2.1. Pharmacokinetics

For Part 1 (IV) the primary estimand for the analyses of the primary PK endpoint will be as defined in Table 5. The same estimand is considered for Part 2 (IM). Part 1 and Part 2 results will be reported separately, and further details will be included in the SAP.

Table 5 Primary Estimand for Primary Pharmacokinetics Endpoint

Primary Estimand	
Variable/Endpoints	PK parameters will be computed using standard non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. From the serum concentration-time data, PK parameters through **Day 29** may include, but are not limited to: • C_{max} • C_{D29} • AUC_{D1-29} • T_{max}, as data permits
Analysis Set	Analysis will be performed using the Pharmacokinetic analysis set, as defined in Section 9.3.
Strategy for Intercurrent Events or Events Leading to Missing Data	Available data will be analyzed as collected regardless of events that may occur (treatment policy).
Summary Measure	Log transformed parameters will be presented with: Geometric mean, 95% confidence interval for the geometric mean, Standard deviation of the log-transformed data (SD logs), Between subject coefficient of variation (%CV_b). Untransformed parameters will be presented with: Arithmetic mean, 95% confidence interval for the arithmetic mean, Standard deviation of the untransformed data (SD), Median, Min, Max.

Supplementary analysis will be performed (if sufficient data is available) to determine the point estimate for the comparison of Japanese to Caucasian participants for each of the PK parameters: C_{max} and AUC_{D1-29}, after adjusting for body weight. The 90% CI based on the geometric least square mean of Japanese:Caucasian participants will also be provided. Analysis will be performed on the Pharmacokinetic analysis set (as defined in Section 9.3) using all available data as collected regardless of any intercurrent events or events resulting to missing data. Further details will be included in the SAP.

In addition, bioavailability analysis will be performed (if sufficient data is available) to determine the point estimate for absolute bioavailability (F_{abs}) after adjusting for body weight and ethnicity. The 90% CI based on the geometric least square mean of test/reference ratio will be provided. Analysis will be performed on the Pharmacokinetic analysis set (as defined in Section 9.3) using all available data as collected regardless of any intercurrent events or events resulting to missing data. The definition of F_{abs} and further details on the planned analyses will be included in the SAP.

Pharmacokinetics data through Day 29 will be displayed in the form of summaries, listings and graphs, where appropriate. Definitions of PK parameters, methods for estimation and details of PK analyses for each study part will be included in the SAP.

9.4.2.2. Safety

For Part 1 (IV), the primary estimand for the analyses of the primary safety endpoints will be as defined in Table 6. The same estimand is considered for Part 2 (IM). Part 1 and Part 2 results will be reported separately.

Table 6 Primary Estimand of the Primary Safety Endpoint

Primary Estimand	
Variable/Endpoints	• Occurrence of AEs through Day 29 • Occurrence of SAEs through Day 29 • Occurrence of AESIs through Day 29 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Day 29 • Occurrence of clinically significant changes in vital signs compared to Baseline through Day 29 • Occurrence of clinically significant laboratory abnormalities through Day 29
Analysis Set	Analysis will be performed using the Safety analysis set, as defined in Section 9.3.
Strategy for Intercurrent Events or Events Leading to Missing Data	Available data will be analyzed as collected regardless of events that may occur (treatment policy).
Summary Measure	Frequency and Percentages

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

9.4.3. Secondary Endpoint(s)

9.4.3.1. Pharmacokinetics

For Part 1 (IV), the primary estimand for the analyses of the secondary PK endpoint will be as defined in Table 7. The same estimand is considered for Part 2 (IM). Part 1 and Part 2 results will be reported separately, and further details will be included in the SAP.

Table 7 Primary Estimand for Secondary Pharmacokinetics Endpoint

Primary Estimand	
Variable/Endpoints	PK parameters will be computed using standard non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. From the serum concentration-time data, PK parameters through **Week 18** may include but are not limited to: • C_{max} • AUC_{inf} • AUC_{last} • T_{max} • T_{last} • $t_{1/2}$, as data permits
Analysis Set	Analysis will be performed using the Pharmacokinetic analysis set, as defined in Section 9.3.
Strategy for Intercurrent Events or Events Leading to Missing Data	Available data will be analyzed as collected regardless of events that may occur (treatment policy).
Summary Measure	Log transformed parameters will be presented with: Geometric mean, 95% CI for the geometric mean. SD logs, Between subject coefficient of variation (%CV_b). Untransformed parameters will be presented with: Arithmetic mean, 95% CI for the arithmetic mean, SD, Median, Min, Max.

Ethnicity comparison for C_{max} and $AUC_{inf,}$ as well as bioavailability analyses, will also be performed as described in Section 9.4.2.1. Further details will be included in the SAP.

Pharmacokinetics data through Week 18 will be displayed in the form of summaries, listings and graphs, where appropriate. Definitions of PK parameters, methods for estimation and details of PK analyses for each study part will be included in the SAP.

9.4.3.2. Safety

For Part 1 (IV), the primary estimand for the analyses of the secondary safety endpoints will be as defined in Table 8. The same estimand is considered for Part 2 (IM). Part 1 and Part 2 results will be reported separately.

Table 8 Primary Estimand of the Secondary Safety Endpoint

Primary Estimand	
Variable/Endpoints	• Occurrence of AEs through Week 18 • Occurrence of SAEs through Week 18 • Occurrence of AESIs through Week 18 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 18 • Occurrence of clinically significant changes in vital signs compared to Baseline through Week 18 • Occurrence of clinically significant laboratory abnormalities through Week 18
Analysis Set	Analysis will be performed using the Safety analysis set, as defined in Section 9.3.
Strategy for Intercurrent Events or Events Leading to Missing Data	Available data will be analyzed as collected regardless of events that may occur (treatment policy).
Summary Measure	Frequency and Percentages

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

9.4.4. Tertiary/Exploratory Endpoint(s)

Incidence and titers (if applicable) of serum ADA and drug-neutralizing antibodies to sotrovimab will be assessed for Part 1 and Part 2. Further details of the analysis methods for the immunogenicity endpoint will be provided in the SAP.

9.5. Interim Analysis

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

However, once the last participant recruited in Part 1 completes the primary assessment (Day 29) the data will be formally unblinded in the systems to allow a readout of the primary endpoints for Part 1. Participants will continue to complete the remaining scheduled assessments up to Week 18. A similar approach may be followed for Part 2 at Day 29. This will be determined at a later stage and details will be included in the planned SAP.

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 International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use (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/IEC
    - 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

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 or designee to submit

complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants 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 copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.

GlaxoSmithKline (alone or working with others) may use 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; publish the results of these research efforts; work with government agencies or insurers to have the 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 or 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. Committees Structure

Not applicable.

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.
- The 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 patients 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, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The Sponsor or 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 Sponsor/GSK Policy.
- The Sponsor/GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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 eCRF completion guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the Integrated Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent Contract Research Organizations (CRO) document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., CRO).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 9 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

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

Table 9 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Hemoglobin			
Coagulation	International Normalized Ratio (INR)	Prothrombin Time (PT)	Activated Partial Thromboplastin Time (aPTT)	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting at Screening and non-fasting at all other timepoints)	Calcium	Alkaline phosphatase[2]	
Urine Testing	• Routine Urinalysis ○ Specific gravity			

	○ pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick ○ Microscopic examination (if blood, protein, or leukocyte esterase is abnormal) • Urine creatinine and urine albumin
Pregnancy testing	• Highly sensitive serum/plasma or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, marijuana, and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5 All events of ALT ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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 diary or form with pre-specified criteria. Unsolicited adverse events are obtained either by asking a general question or unprompted 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 hospitalisation, 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 local at the injection site and systemic events for which the participant is specifically questioned.

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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.
- 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.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT ≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or 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. 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 GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- 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 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.

Table 10 should be used to grade the severity of an AE that is not specifically identified in the grading tables within *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, version 2.1 (July 2017). In addition, CCI [redacted] CCI [redacted] are to be classified as Grade 5.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE as per Section 10.3.2, NOT when it is rated as severe.

Table 10 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Not Otherwise Specified in DAIDS version 2.1

PARAMETER	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.				

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 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.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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 72 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 medical monitor by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual (SRM).

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (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 (at least 1 week apart) is required.
    - Females on HRT and whose menopausal status is in doubt 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., 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.

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

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, (e.g., 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 follicle stimulating hormone (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 (at least 1 week apart) is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) 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.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver Chemistry Monitoring Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Monitoring Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or INR >1.5, report to GSK as an SAE[1,2].</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within Baseline (see MONITORING)
MONITORING:
If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within Baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND total bilirubin < 2xULN and INR ≤1.5:
• Perform liver chemistries (include ALT,</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 127 days of the most recent dose[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications.
• Record alcohol use on the liver event alcohol intake form</td></tr>
</table>

Liver Chemistry Monitoring Criteria	
AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within Baseline	**If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable**, record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported **to GSK** as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and hepatitis B core antibody (HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6. Appendix 6: Management of Local Injection Site Reactions and Systemic Symptoms (Anaphylaxis)

A. Local Injection Site Reactions

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

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

B. Systemic Reactions/Anaphylaxis

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

Diagnosis of Anaphylaxis

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

Danger Signs include:

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

Management of Anaphylaxis

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

1. Call for additional medical assistance; activate emergency medical services
2. Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry
3. First-line treatment:

   Administer epinephrine (1.0 mg/mL) aqueous solution (1:1000 dilution) – 0.5 mg (0.5 mL) IM in the anterolateral thigh
   If using an epinephrine auto-injector – use 0.3 mg IM into the anterolateral thigh
   May be repeated every 5-15 minutes up to 3 times
4. Optional treatment (antihistamine):

   Diphenhydramine 50 mg oral/IV/IM

   OR

   Hydroxyzine 25 mg oral/IM
5. Give oxygen (8-10 L/minute) via facemask, as needed
6. Normal saline rapid bolus – treat hypotension with rapid infusion of 1-2 liters IV
7. Monitor patient until emergency medical services arrive.

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10.7. Appendix 7: Abbreviations and Definitions and Trademarks

Term	Definition
µg	Micrograms
$\%AUC_{exp}$	The extrapolated portion of AUC_{inf}
%CV	Percent coefficient of variation
$\%CV_b$	Between subject coefficient of variation
ADA	Anti-drug antibody
ADE	Antibody dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
AIH	Autoimmune hepatitis
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the curve
AUC_{D1-29}	Area under the serum-concentration time curve from Day 1 to Day 29
AUC_{inf}	Area under the serum concentration-time curve extrapolated to infinite time
AUC_{last}	Area under the curve from the time of dosing to the time of the last measurable (positive) concentration
BMI	body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CA	Competent Authority
C_{D29}	Concentration at Day 29
C_{last}	Observed concentration corresponding to T_{last}.
C_{max}	Maximum observed serum concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form

Term	Definition
CRO	Contract research organization
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DAIDS	Division of acquired immune-deficiency syndrome
DILI	Drug induced liver injury
DSMB	Data and Safety Monitoring Board
EC	Ethics committee
EC_{90}	90% effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early discontinuation
EDC	Electronic data capture
EOS	End of study
EUA	Emergency use authorization
EW	Early withdrawal
FcγR	Fc Gamma Receptor
F_{abs}	Absolute bioavailability
FI	Formalin-inactivated
FSH	Follicle stimulating hormone
GCSP	Global Clinical Safety and Pharmacovigilance
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
HSR	Hypersensitivity reactions
IB	Investigator's brochure

Term	Definition
ICF	Informed consent form
ICH	International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgG1κ	Immunoglobulin G1 kappa
IgM	Immunoglobulin M
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional review board
IRR	Infusion related reaction
ISR	Injection site reaction
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	Interactive Web Response System
JSRT	Joint safety review team
kg/m^2	Kilograms per meter square
L	Liter
LAM	Lactational amenorrhea method
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MARM	Monoclonal antibody-resistant mutant
MCH	Mean corpuscular volume
MCV	Mean corpuscular hemoglobin
Max	Maximum
Min	Minimum
mg	Milligram
mL	Milliliter
mm/Hg	Millimeter of mercury
MSDS	Material safety data sheet

Term	Definition
NQ	Non-quantifiable
PI	Principal investigator
PK	Pharmacokinetic(s)
PR	Pulse rate
PT	Prothrombin time
QTc	Corrected QT interval
QTLs	Quality tolerance limits
RBC	Red blood cell count
RNA	Ribonucleic acid
RR	Respiratory rate
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-1	Severe acute respiratory syndrome coronavirus-1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SAP	Statistical analysis plan
SD	Standard deviation of the untransformed data
SD logs	Standard deviation of the log-transformed data
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of activities
SpO2	Oxygen saturation
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal elimination half-life
T_{last}	Time of the last quantifiable concentration
T_{max}	Time to reach C_{max}
TBD	To be determined
ULN	Upper limit of normal
US	United States
V	Apparent volume of distribution
Vir	Vir Biotechnology, Inc.
WBC	White blood cell

Term	Definition
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of non-childbearing potential
V_z	Volume of distribution during the elimination
λz	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve.

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
None

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