Protocol

Study ID: 216912

Official Title of Study: A Multicenter, Randomized, Double-Blind, Parallel Group Phase II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of a Second Generation VIR-7831 Material in Non-Hospitalized Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)

NCT ID: NCT04779879

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TITLE PAGE

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Protocol Number: GSK Study 216912 (VIR-7831-5006) / Amendment 05

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

Brief Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of second generation VIR-7831 material administered intravenously (IV) and intramuscularly (IM) in non-hospitalized participants with mild to moderate coronavirus disease 2019 (COVID-19)

Study Phase: Phase II

Acronym: COMET-PEAK (**CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial – **P**atient saf**E**ty, toler**A**bility, pharmaco**K**inetics)

Sponsor Name and Legal Registered Address:

Vir Biotechnology, Inc.
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USA

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

Regulatory Agency Identifying Number(s):

IND: 149315

EudraCT: 2021-000724-35

NCT: NCT04779879

Approval Date: 29-OCT-2021

SPONSOR SIGNATORY:

Protocol Title: A Multicenter, Randomized, Double-Blind, Parallel Group Phase II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of a Second Generation VIR-7831 Material in Non-Hospitalized Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)

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Elizabeth Alexander, MD, MSc	**Date**
Vice President, Clinical Research	
Vir Biotechnology Inc.	

The signed page is a separate document.

Medical Monitor Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 05	29-OCT-2021	TMF-14113476
Amendment 04	18-MAY-2021	TMF-12902987
Amendment 03	08-APR-2021	TMF-11941318
Amendment 02	03-MAR-2021	TMF-11814330
Amendment 01	19-JAN-2021	TMF-11735674
Original Protocol	10-DEC-2020	2020N457654_00

Amendment 05: 29-OCT-2021

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

Overall Rationale for the Amendment: Expanded the safety follow-up of all active participants through Week 36 (~5 half lives of sotrovimab).

Section # and Name	Description of Change	Brief Rationale
Section 1:Brief Summary, Objective/Endpoints, Schema, SoA: Part A, Part B, Part C, 2.3.1 Risk Assessment Table, 3 Objectives/Endpoints, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 4.4 End of Study Definition, 5.1. Inclusion Criteria, 8 Study assessments, 8.4. Safety Assessments, 8.4.5 Active Monitoring of COVID-19 Progression, 8.5.1 Time Period and Frequency for Collecting AE, and SAEs, 8.5.6. Pregnancy 8.5.8 Disease-Related Events and/or Disease-Related Outcomes not Qualifying as AE or SAE, 8.5.9.4 Antibody-Dependent Enhancement, 9.4.3 Secondary Endpoints.	Added a site phone call at Week 36 to all to capture SAEs, AESIs, DREs, concomitant medication, COVID symptoms and pregnancy status. Added instructions for all WOCBP to continue contraception through Week 36.	Given that the half-life of sotrovimab is approximately 49 days a decision was made to expand the safety follow-up through Week 36 (~5 half-lives).
2.3.3. Overall Benefit:Risk Conclusion, 6.1. Table 5	Correction of a reference and clarification in the table to include Gen2 IM as a source.	General administrative updates.
Throughout document	Other minor grammatical and typographical corrections.	To improve readability

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Multicenter, Randomized, Double-Blind, Parallel Group Phase II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of a Second Generation VIR-7831 Material in Non-Hospitalized Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)

Brief Title:

Safety, tolerability, pharmacokinetics, and pharmacodynamics of second generation VIR-7831 material administered intravenously (IV) and intramuscularly (IM) in non-hospitalized participants with mild to moderate coronavirus disease 2019 (COVID-19)

Rationale:

There is an urgent medical need for therapeutics for the treatment of coronavirus disease 2019 (COVID-19).

Vir Biotechnology, Inc. (Vir) is developing VIR-7831 (also known as GSK4182136, sotrovimab) for the treatment and prophylaxis of COVID-19. VIR-7831 is a human immunoglobulin G (IgG1) monoclonal antibody (mAb) that binds to a highly conserved epitope on the spike protein receptor binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

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

COMET-ICE, is a seamless first-in-human (FIH) Phase II/III study assessing the safety and efficacy of a single 500 mg intravenous dose of VIR-7831 for the early treatment of COVID-19 in non-hospitalized participants at high risk for progression and subsequent hospitalization. Participants were randomized in a 1:1 ratio to VIR-7831 or placebo. COMET-ICE started with a lead-in phase (N=21) in August 2020 to assess safety and tolerability. An Independent Data Monitoring Committee (IDMC) met 23 September 2020 to review unblinded safety data after the 20th participant from the lead-in cohort completed Day 15 (1 participant was withdrawn). There were no deaths or serious adverse events reported up to this IDMC review. The IDMC recommended the study to proceed with the expansion-phase to enroll additional participants across each treatment group (~1300 participants total).

Subsequently, the IDMC met to review available safety and tolerability data on 28 January 2021. At the data cutoff of 22 January 2021, safety data was available from

526 participants (of 532 enrolled) including 405/532 (76%) who were at least 15 days post-dosing. Available data indicate that 99/526 (19%) participants experienced an adverse event (AE) with 10 (2%) participants experiencing an AE related to study treatment. One participant experienced a serious adverse event (SAE) of respiratory distress with onset 10 days after study drug infusion that led to patient discontinuation from the study follow up. This event occurred on Day 12 and resolved on Day 27, lasting 16 days. In the validated dataset shared with the IDMC, there were 22 SAEs reported, the majority of which represented respiratory progression of COVID-19 disease leading to hospitalization (i.e. disease progression) which is also the primary efficacy endpoint. Of these, one participant of the 526 for whom safety data was available (<1%) experienced an SAE coded to Preferred Term Covid-19, which was later updated to Covid-19 pneumonia, and was considered related. The IDMC recommended the study to continue with no adaptation.

The IDMC subsequently met on 10 March 2021 for a planned interim analysis, with review of data from 583 participants. There was an 85% reduction in the primary endpoint of hospitalization or death in the VIR-7831 arm versus the placebo arm (p=0.002). The IDMC recommended that the study halt enrollment on the basis of overwhelming efficacy [Vir Biotechnology, 2021].

VIR-7831 was also being studied for the treatment of hospitalized participants with COVID-19 in Study 215149, also known as ACTIV-3-TICO, sponsored by the National Institute of Allergy and Infectious Diseases. The ACTIV-3-TICO study is a randomized, blinded, placebo-controlled platform study that allows investigational drugs to be added and dropped during the course of the study. The sub-study evaluating VIR-7831 started in December 2020 and aimed to enroll approximately 500 participants per treatment arm.

A Data and Safety Monitoring Board (DSMB) review for ACTIV-3-TICO to include the VIR-7831 sub-protocol occurred on 25 January 2021. The DSMB reviewed data from 148 participants who had been randomized to VIR-7831 or shared placebo. One potentially life-threatening allergic reaction (anaphylaxis) was reported during infusion in ACTIV-3-TICO in a participant who received VIR-7831. 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 VIR-7831 sub-study should continue as planned.

The DSMB met on 01 March 2021 for a pre-planned safety and efficacy data review of ACTIV-3-TICO. While VIR-7831 met initial pre-specified criteria to continue to the next phase of the ACTIV-3 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, 2021a].

To date, partial Phase 1 pharmacokinetics (PK) data from Lead-in subjects enrolled in COMET-ICE is available through Study Day 57. The mean maximum concentration (C_{max}) of 500 mg VIR-7831 was 219 µg/mL following a 1 hour IV infusion. The mean serum level on Day 29 is 37.2 µg/mL for the Lead-in phase of COMET-ICE.

Vir partnered with WuXi Biologics to initiate manufacturing activities to enable rapid entry of VIR-7831 into the COMET-ICE (NCT04545060) study in non-hospitalized patients with mild to moderate disease in August 2020. Initially, two manufacturing batches were produced from a pool of cells (non-clonal) stably transfected to express the VIR-7831 sequences (Generation 1 [Gen1]). Additional cGMP drug substance has been produced at WuXi Biologics using a similar manufacturing process but from a clonal Master Cell Bank (MCB) derived from the original pool of transfectants (Generation 2 [Gen2]). As Gen2 is from a clonally-derived cell bank, it will be the intended commercial product.

COMET-ICE and ACTIV-3-TICO utilized Gen1 material. Analytical comparability studies evaluating Gen1 drug substance (DS) and drug product (DP) in relation to Gen2 DS and DP have recently been completed. These studies included routine release analysis and extended characterization, and were designed and completed in alignment with International Council for Harmonisation (ICH) Q5E guidelines (comparability of biotechnological/biological products subject to changes in their manufacturing process). These confirm a high degree of analytical and bioanalytical comparability between Gen1 and Gen2, thereby supporting the use of Gen2 in clinical studies.

In addition, Gen2 IV material was used in combination with bamlanivimab, in one arm of the BLAZE-4 study (NCT04634409), a clinical trial with multiple arms evaluating anti-SARS-CoV-2 mAbs from Eli Lilly and Company. In this arm, the combination of bamlanivimab with VIR-7831 was compared 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 February 2021. As of 17 March 2021, no safety concerns have been identified. 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 VIR-7831 500 mg. Co-administration of bamlanivimab and VIR-7831 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 [GlaxoSmithKline plc, 2021b].

Since Gen2 will be the commercial product, Vir is proposing this study to gain additional clinical experience with Gen2 administered both intravenously (IV) and via intramuscular (IM) injection in non-hospitalized patients with mild to moderate COVID-19, a patient population similar to that of COMET-ICE, to complement the analytical and bioanalytical data. This study will evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and viral pharmacodynamics (PD) of both IV and IM formulations of VIR-7831 Gen2 (500 mg IV, 500 mg IM and 250 mg IM) when administered in this early treatment population. Part A of the study will evaluate VIR-7831 Gen2 and Gen1 500 mg administered via IV infusion. Part B will evaluate VIR-7831 Gen2 500 mg IV infusion and Gen2 500 mg IM injection, and Part C will evaluate VIR-7831 Gen2 500 mg IV infusion and Gen2 250 mg IM injection. Intramuscular injection of VIR-7831 will also be evaluated in the following planned studies:

- A study evaluating efficacy, safety, and tolerability of VIR-7831 IM (250 mg and 500 mg) versus VIR-7831 IV (500 mg) for treatment of mild/moderate COVID-

19 in non-hospitalized participants at high risk for disease progression (VIR-7831-5008 [GSK Study 217114] also known as COMET-TAIL)

- Studies evaluating VIR-7831 IM (500 mg) as prophylaxis against SARS-CoV-2 infection.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Safety (Part A) To evaluate the safety and tolerability profile of intravenous (IV) VIR-7831 Gen2 and IV Gen1	• 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 disease progression events (not classified as AEs) through Day 29
Pharmacodynamics (Part B) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via intramuscular (IM) injection (500 mg) in the upper respiratory tract	• Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUC_{D1-8}) in nasopharyngeal swab samples
Pharmacodynamics (Part C) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via IM injection (250 mg) in the upper respiratory tract	• Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUC_{D1-8}) in nasopharyngeal swab samples
Secondary	
Safety (Part A) To evaluate the safety and tolerability profile of IV VIR-7831 Gen2 and IV Gen1	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 36 • Occurrence of AESIs through Week 36

Objectives	Endpoints
	• Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 36
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, 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 disease progression events (not classified as AEs) through Day 29
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, through End of Study (EOS)	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 36 • Occurrence of AESIs through Week 36 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 36
Virology (Part A) To characterize the effect of VIR-7831 Gen2 IV and Gen1 IV on the viral shedding profile in the upper respiratory tract	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from saliva and nasal mid-turbinate swabs samples
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and Gen2 IM on the viral shedding profile in the upper respiratory tract	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from nasopharyngeal (NP) swab samples • Proportion of participants with undetectable viral load at all visits through Day 29 of the study as measured by qRT-PCR from NP swab samples

Objectives	Endpoints
	• Mean area under the curve of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 5 (AUC_{D1-5}) and Day 1 to 11 (AUC_{D1-11})
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and IM on viral load clearance in the upper respiratory tract	• Proportion of individuals with a persistently high viral load at Day 8 as assessed via qRT-PCR in NP swab samples (see Section 8.3)
Pharmacokinetics (Part A, Part B, and Part C) To assess the pharmacokinetics (PK) of VIR-7831 Gen2 IV and IM and Gen1 IV in serum	• Serum PK of VIR-7831
Exploratory	
Resistance (Part A, Part B, and Part C) To monitor the presence at Baseline and the emergence of SARS-CoV-2 resistant mutants against VIR-7831	• Presence at Baseline and emergence of SARS-CoV-2 viral resistance mutants
Immunogenicity (Part A, Part B , and Part C) To assess the immunogenicity of VIR-7831 Gen2 IV and IM and Gen1 IV	• Incidence and titers (if applicable) of serum anti-drug antibodies (ADA) to VIR-7831
Immunology (Part A, Part B and Part C) To assess the effect of VIR-7831 Gen2 IV and IM and Gen1 IV on immune response	• Incidence and titers (if applicable) of anti-nucleocapsid (anti-N), anti-spike (anti-S) and anti-receptor binding domain (anti-RBD) SARS-CoV-2 antibodies at baseline • Incidence and titers (if applicable) of anti-N SARS-CoV-2 antibodies at Day 29

Overall Design:

This study is a randomized, multi-center, parallel group phase II trial of VIR-7831, a monoclonal antibody (mAb) against SARS-CoV-2, in non-hospitalized patients with mild to moderate COVID-19, aged 18 years or older. The study is comprised of Parts A, B, and C.

Part A Design:

Part A of the study is double-blind and participants will be randomized 3:1 to receive a single, 500 mg intravenous infusion of either Gen2 or equal volume Gen1 study material. A Gen1 study arm is included to maintain blinding of Gen1 versus Gen2 VIR-7831 receipt during the conduct of the study, including for assessment of safety outcomes. Safety, tolerability, virology, immunogenicity, and PK will be evaluated.

Part B Design:

Part B of the study will be open-label and participants will be randomized 1:1 to receive a 500 mg dose of Gen2 material by IV infusion or intramuscular (IM) injection. In Part B, viral load PD as assessed via upper respiratory samples, safety, tolerability, immunogenicity, and PK will be evaluated. Part B will include a Lead-in phase (n=20) with frequent assessments for injection site reactions (ISRs), infusion-related reactions (IRRs), and safety, along with PK sampling.

A JSRT review on 13 May 2021 identified no serious safety concerns on review of 66 participants enrolled in Part B (all of the Lead-in participants and some Expansion phase participants). Based on this safety review, the Joint Safety Review Team (JSRT) agreed with the proposal to reduce the post-dose monitoring time on Day 1 from 2 hours to 1 hour for Part B of the study.

Part C Design:

Part C of the study will be open-label and participants will be randomized 1:1 to receive a 500 mg dose of Gen2 material by IV infusion or a 250 mg dose of Gen2 material by IM injection. Participants will be stratified by prior exposure to an authorized or approved SARS-CoV-2 vaccine. In Part C, viral load PD as assessed via upper respiratory samples, safety, tolerability, immunogenicity, and PK will be evaluated. Part C will include a Lead-in phase (n=20) with frequent safety assessments to allow for JSRT determination if the post-dose monitoring time can be shortened (from 1 hour to 30 minutes). The Lead-in phase will also include PK sampling.

Brief Summary:

This study will occur in 3 Parts (Part A, Part B, and Part C). The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and viral PD of the Gen2 VIR-7831 material. All participants will receive standard of care (SoC) for COVID-19 disease during this study, including admission to a hospital if deemed necessary by the responsible investigator.

Enrollment for Part A of the study, which assesses intravenous (IV) Gen2, will commence first. Enrollment for Part B of the study, which assesses 500 mg IV and 500 mg IM Gen2, will not be gated to Part A. Enrollment for Part C of the study, which will assess Gen2 500 mg IV and Gen2 250 mg IM, will not be gated to Part A or Part B.

Part A:

- Treatment Duration: Single IV infusion on Day 1.
- Day 1 monitoring: Approximately 9 hours for safety assessments and intensive PK sampling.
- Study Duration: 36 weeks.
- Blinded JSRT will review all available safety data at regular intervals. While the primary safety endpoint is through Day 29, safety assessments will continue during the study to end-of-study (EOS) (Week 36).

After Day 1, subsequent visits for study activities and clinical monitoring will be conducted via clinic visits (except for Week 16 and Week 36, which will be a phone call).

Part B:

- Treatment Duration: Single-dose by IV infusion or IM injection on Day 1.
- Day 1 monitoring: Approximately 2 hours post-dose in the Lead-in phase and 1 hour post-dose in the Expansion phase (based on JSRT review) for safety assessments.
- Study Duration: 36 weeks.
- JSRT will review all available safety data at regular intervals. The JSRT will review unblinded aggregate safety and tolerability data by treatment arm through Day 3 for the Lead-in phase participants (n=20). Enrollment for Part B of the study will continue into the Expansion phase once the Lead-in (n=20) has been recruited, but Day 1 monitoring will remain at 2 hours post-dose for new participants until the JSRT provides a recommendation that this monitoring in the Expansion phase can be shortened to 1 hour post-dose.
- After Day 1, subsequent visits for study activities and clinical monitoring will be conducted via home or clinic visits (except for Week 6,Week 16, and Week 36 for both the Lead-in phase and Expansion phase, and Week 8 for the Expansion phase, which will be phone calls).

A JSRT review on 13 May 2021 identified no serious safety concerns on review of 66 participants enrolled in Part B (all of the Lead-in participants and some Expansion phase participants). Based on this safety review, the JSRT agreed with the proposal to reduce the post-dose monitoring time on Day 1 from 2 hours to 1 hour for Part B of the study.

Part C:

- Treatment Duration: Single-dose by IV infusion or IM injection on Day 1.
- Day 1 monitoring: Approximately 1 hour post-dose in the Lead-in phase and 30 minutes post-dose in the Expansion phase (based on JSRT review) for safety assessments.
- Study Duration: 36 Weeks.
- The JSRT will review all available safety data at regular intervals. The JSRT will review unblinded aggregate safety and tolerability data by treatment arm through

Day 3 for the Lead-in phase participants (n=20). Enrollment for Part C of the study will continue into the Expansion phase once the Lead-in (n=20) has been recruited, but Day 1 monitoring will remain at 1 hour post-dose for new participants until the JSRT provides a recommendation that this monitoring in the Expansion phase can be shortened to 30 minutes post-dose.

- After Day 1, subsequent visits for study activities and clinical monitoring will be conducted via home or clinic visits (except for Week 6,Week 16 and Week 36 for both the Lead-in phase and Expansion phase, and Week 8 for the Expansion phase, which will be phone calls).

Number of Participants:

Part A:
Approximately 40 enrolled participants 18 years of age or older will be randomly assigned in a 3:1 (Gen2: Gen1) randomization scheme to study intervention. Any participant who receives the study intervention will be considered evaluable.

Part B:
Part B will enroll a total of approximately 150 participants 18 years to <70 years of age with a detectable viral load at baseline (Day 1).

In the Lead-in phase of Part B, approximately 20 participants will be enrolled and randomly assigned (1:1) to receive either Gen2 500 mg IV or Gen2 500 mg IM. An unblinded review of injection site reactions (ISRs), infusion-related reactions (IRRs), and other safety and tolerability data through Day 3 will be performed by the JSRT.

Enrollment for the Expansion phase will begin after completion of enrollment of the Lead-in phase; however, the change from 2 hours to 1 hour of monitoring post-injection or post-infusion did not occur until after the JSRT recommendation to reduce the monitoring time was received on 13 May 2021, following review of the Day 3 data from the Lead-in phase. In the Expansion phase, approximately 130 participants will be randomly (1:1) assigned to receive Gen2 500 mg IV or Gen2 500 mg IM. Any participant who receives the study intervention will be considered evaluable.

A greater number of participants may be enrolled in the Part B Expansion phase if blinded assessments of baseline (Day 1) viral load data that are available from Part A of the study and the Lead-in phase of Part B (anticipated total of 40 to 60 baseline viral loads from the two parts combined) demonstrate that there are individuals with an undetectable viral load at baseline. If it is determined that additional participants will need to be enrolled, the expected total enrollment will be updated based on estimates of the percentage of participants with undetectable virus at baseline using data from participants in Part A and the Part B Lead-in phase. In this event, additional participants will be enrolled up to a maximum of 110 per arm (220 total for Part B) and randomized 1:1 to Gen2 500 mg IV or IM to achieve approximately 75 participants per arm in Part B with a detectable viral load at baseline.

Part C:

Part C will enroll a total of approximately 150 participants 18 years to <70 years of age with a detectable viral load at baseline (Day 1).

In the Lead-in phase of Part C, approximately 20 participants will be enrolled and randomly assigned (1:1) to receive either Gen2 500 mg IV or Gen2 250 mg IM. An unblinded review of ISRs, IRRs, and other safety and tolerability data through Day 3 will be performed by the JSRT.

Enrollment for the Part C Expansion phase will begin after completion of enrollment of the Lead-in phase; however, the change from 1 hour to 30 minutes of monitoring post-injection or post-infusion will not occur until a recommendation to reduce monitoring time from the JSRT is received, following review of the Day 3 data from the Lead-in phase. In the Expansion phase, approximately 130 participants will be randomly (1:1) assigned to receive Gen2 500 mg IV or Gen2 250 mg IM. Any participant who receives the study intervention will be considered evaluable.

A greater number of participants may be enrolled in the Part C Expansion phase if blinded assessments of baseline (Day 1) viral load data that are available from Part A of the study and the Lead-in phase of Part B (anticipated total of 40 to 60 baseline viral loads from the two Parts combined) demonstrate that there are individuals with an undetectable viral load at baseline. If it is determined that additional participants will need to be enrolled, the expected total enrollment will be updated based on estimates of the percentage of participants with undetectable virus at baseline using data from participants in Part A and the Part B Lead-in phase. In this event, additional participants will be enrolled up to a maximum of 110 per arm (220 total for Part C) and randomized 1:1 to Gen2 500 mg IV or Gen2 250 mg IM to achieve approximately 75 participants per arm in Part C with a detectable viral load at baseline.

Note: For all study Parts, "enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Part A:
Screening assessments will be performed within 1 day before the start of infusion. After completion of screening and baseline assessments, eligible participants will be randomized in a 3:1 ratio to VIR-7831 Gen2 or Gen1, by interactive response technology (IRT) in a blinded manner and treated with a single IV dose of the study intervention on Day 1. Screening may be performed on the same day as randomization and dosing (Day 1). All participants will receive SoC as per institutional protocols, in addition to the study intervention.

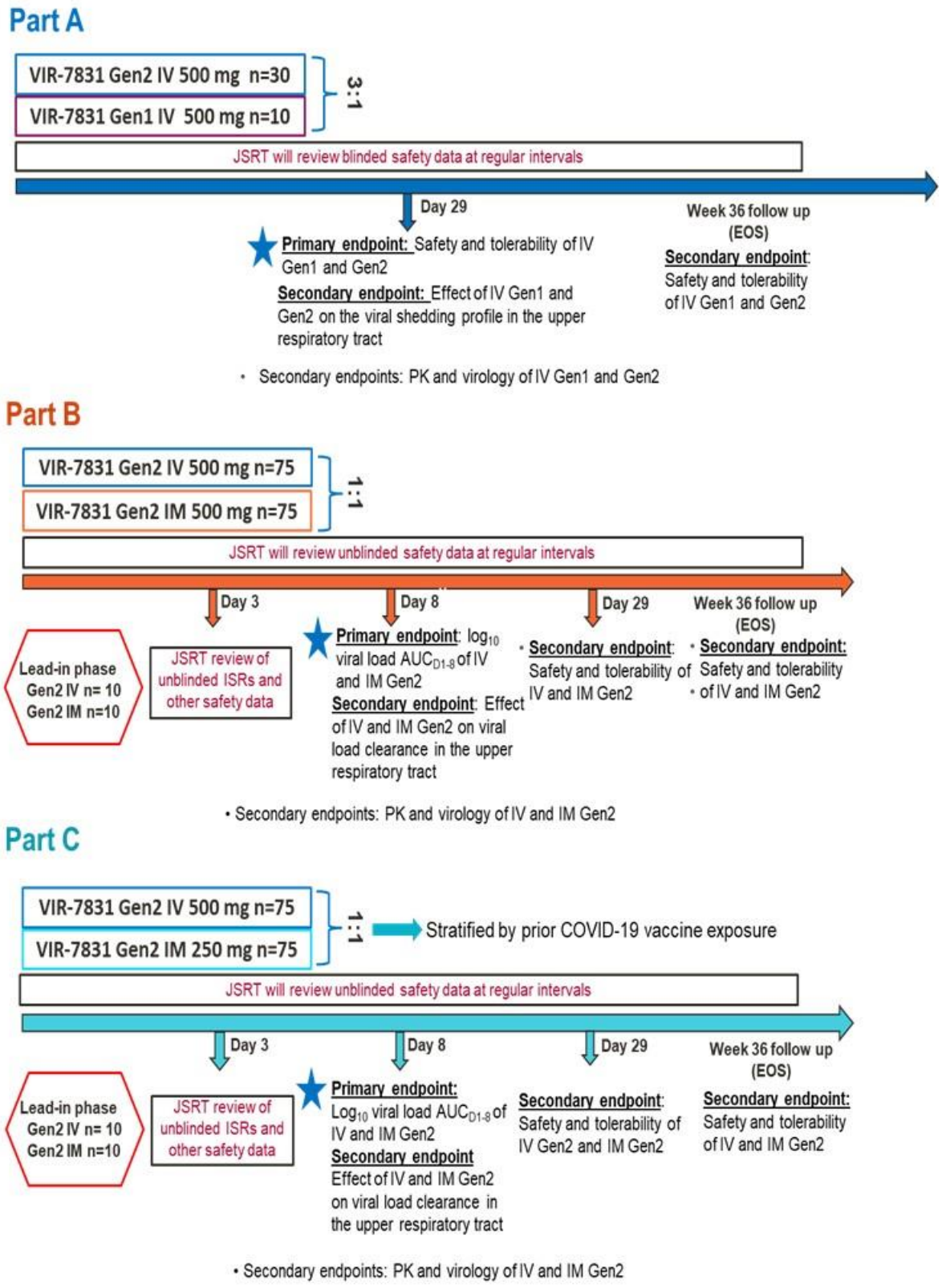
Part B:
Screening assessments will be performed within 1 day before the start of the IV infusion or IM injections. After completion of screening and baseline assessments, eligible participants will be randomized in a 1:1 ratio to receive a single dose of VIR-7831 Gen2 IV (500 mg) or Gen2 IM (500 mg), by IRT on Day 1. Part B will be open-label, and participants will only receive the intervention that he/she is randomized to receive (i.e., there is no additional placebo administered IV or IM). Screening may be performed on the same day as randomization and dosing (Day 1). All participants will receive SoC as per institutional protocols, in addition to the study intervention.

Part C:
Screening assessments will be performed within 1 day before the start of the IV infusion or IM injections. After completion of screening and baseline assessments, eligible participants will be randomized in a 1:1 ratio to receive a single dose of VIR-7831 Gen2 IV (500 mg) or Gen2 IM (250 mg), by IRT on Day 1. Part C will be open-label, and participants will only receive the intervention that they are randomized to receive (i.e., there is no additional placebo administered IV or IM). Screening may be performed on the same day as randomization and dosing (Day 1). All participants will receive SoC as per institutional protocols, in addition to the study intervention.

Joint Safety Review Team (JSRT):

The JSRT, comprised of team members from clinical research, pharmacovigilance and statistics from Vir and GSK, will review blinded safety data from Part A of the study at regular intervals. For Parts B and C of the study, the JSRT will be unblinded, and data will be reviewed according to the Treatment-Sensitive Data Plan for Open-Label Randomized Study. There will be no routine in-stream review of aggregated safety data by treatment arm at any JSRT meeting other than at the two post-Day 3 JSRT meetings (one for Part B and one for Part C) that will determine if the monitoring time may be reduced. Additionally, any sharing of potential safety signals will reflect pooled data that is not separated by treatment arm. The Safety team may need to review single unblinded case reports to support regulatory reporting obligations and/or potential safety signals that may need to be reviewed by JSRT. The objective nature of the primary endpoint (virologic PD) further supports the central team and JSRT remaining unblinded. Details regarding the JSRT process will be available in relevant Safety Review Team (SRT) documents.

1.2. Schema


Part A
VIR-7831 Gen2 IV 500 mg n=30
VIR-7831 Gen1 IV 500 mg n=10
3:1
JSRT will review blinded safety data at regular intervals
Day 29
Primary endpoint: Safety and tolerability of IV Gen1 and Gen2
Secondary endpoint: Effect of IV Gen1 and Gen2 on the viral shedding profile in the upper respiratory tract
Week 36 follow up (EOS)
Secondary endpoint: Safety and tolerability of IV Gen1 and Gen2
• Secondary endpoints: PK and virology of IV Gen1 and Gen2
Part B
VIR-7831 Gen2 IV 500 mg n=75
VIR-7831 Gen2 IM 500 mg n=75
1:1
JSRT will review unblinded safety data at regular intervals
Day 3
Day 8
Day 29
Week 36 follow up (EOS)
Lead-in phase Gen2 IV n= 10 Gen2 IM n=10
JSRT review of unblinded ISRs and other safety data
Primary endpoint: log10 viral load AUCD1-8 of IV and IM Gen2
Secondary endpoint: Effect of IV and IM Gen2 on viral load clearance in the upper respiratory tract
• Secondary endpoint: Safety and tolerability of IV and IM Gen2
• Secondary endpoint: Safety and tolerability of IV and IM Gen2
• Secondary endpoints: PK and virology of IV and IM Gen2
Part C
VIR-7831 Gen2 IV 500 mg n=75
VIR-7831 Gen2 IM 250 mg n=75
1:1
Stratified by prior COVID-19 vaccine exposure
JSRT will review unblinded safety data at regular intervals
Day 3
Day 8
Day 29
Week 36 follow up (EOS)
Lead-in phase Gen2 IV n= 10 Gen2 IM n=10
JSRT review of unblinded ISRs and other safety data
Primary endpoint: Log10 viral load AUCD1-8 of IV and IM Gen2
Secondary endpoint Effect of IV and IM Gen2 on viral load clearance in the upper respiratory tract
Secondary endpoint: Safety and tolerability of IV Gen2 and IM Gen2
Secondary endpoint: Safety and tolerability of IV and IM Gen2
• Secondary endpoints: PK and virology of IV and IM Gen2

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities: Part A

			W1			W2			W3	W4	W6	W8	W12	W16	W20	W24	W36	Notes
	Study Visit Day ± Visit Window[14]	**Screening (Day 0/1)**	**Day 1**	**Day 2**	**Day 5**	**Day 8**	**Day 11**	**Day 15 ± 1d**	**Day 22 ± 1d**	**Day 29 ± 2d**	**Day 43 ± 3d**	**Day 57 ± 4d**	**Day 85 ± 7d**	**Day 113 ± 7d**	**Day 141 ± 7d**	**Day 169 ± 7d**	**Day 253 ± 7d**	
	Site visit or call[1]	Site	Site	Site	Site	Site	Site	Site	Site	Site	Site	Site	Site	Call[1]	Site	Site	Call	1. The site phone call may be replaced with a clinic visit at the discretion of the investigator.
Screening only	Informed consent	X																2. Data on the history of COVID-19 illness prior to enrollment should be collected in the specific eCRF.
Screening only	Demography	X																3. As per institution diagnostic protocols.
Screening only	COVID-19 Disease History[2]	X																4. All screening procedures must be completed within 1 day prior to dosing. Screening and dosing may take place on the same day.
Screening only	Medical history (incl. comorbidities and tobacco use)	X																5. Including height and weight.
Screening only	SARS-CoV-2 diagnostic test (if not previously confirmed)[3]	X																6. If screening and dosing occur on the same day: full physical examination, pre-treatment vital signs, and pre-treatment safety lab assessments only need to be performed once, and only the triplicate ECGs prior to infusion are required; an additional single 12-lead ECG prior to infusion is not required.
	Randomization[4]		X															
	Study intervention administration		X															
Assessments	Full physical examination	X[5,6]	X															
Assessments	COVID-19 signs/symptoms review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessments	Vital Signs (BP, PR, RR, temperature and oxygen saturation)	X[6]	X[7]	X	X	X	X	X	X	X						X		7. Record Day 1 vital signs: prior to dosing, then every 15 minutes during IV infusion, and at approximately 1, 2, 6, and 8 hours after end of infusion. Vital signs on other days should be performed once daily.
Assessments	12-lead ECG[8]	X[6]	X		X		X						X					8. Day 1: triplicate ECGs prior to infusion and within 30 minutes of end of infusion. All other timepoints are single 12-lead ECG once daily.
Sample collection	Safety lab assessments	X[6]	X[9]	X[9]	X	X												
Sample collection	Pregnancy test[10]	X														X		9. Urine for albumin to creatinine ratio should be collected on Day 1 (pre-dose) and on Day 2. Other safety labs on Day 1 should also be collected pre-dose.
Sample collection	Blood sample for PK analysis[11]		X[11]	X	X	X		X		X	X	X	X		X	X		10. Urine or serum pregnancy test, as required by local guidelines. Refer to Section 8.4.7.
Sample collection	Blood sample for anti-drug antibody		X[12]							X			X		X	X		11. On Day 1, sample collection will occur pre-dose, end of infusion and at approximately 1, 2, 6, and 8 hours following end of infusion. On other days, samples will be collected once daily.
Sample collection	Nasal mid-turbinate swab for virology		X[12]	X	X	X	X	X	X	X								12. On Day 1, sample collection will occur pre-dose.
Sample collection	Saliva sampling for virology		X[12]	X	X	X	X	X	X	X								13. At screening, only SAEs related to study participation or a GSK product will be reported.
Sample collection	Blood sample for Anti-SARS-CoV-2 antibody (serum)		X[12]							X								14. If participant withdraws early from the study prior to Week 24, then the W24 visit assessments will be performed as the EW visit. If the participant withdraws early from the study after Week 24, the W36 visit assessments will be performed as the EW visit.
Sample collection	AE review		<========== X ==========>															
Sample collection	SAE review	X[13]		<========== X ==========>														
Sample collection	AESI, disease-related events, and concomitant medication review			<========== X ==========>														

Table 2 Schedule of Activities: Part B

	Study Visit Day ± Visit Window[17]	Screening (Day 0/1)	W1 Day 1	W1 Day 2	W1 Day 3	W1 Day 5	W2 Day 8	W2 Day 11	W2 Day 15 ± 1d	W3 Day 22 ± 1d	W4 Day 29 ± 2d	W6 Day 43 ± 3d	W8 Day 57 ± 4d	W12 Day 85 ± 7d	W16 Day 113 ± 7d	W20 Day 141 ± 7d	W24 Day 169 ± 7d	W36 Day 253 ± 7d
	Site visit[1], home visit[1], or call[2]	Visit	Visit	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Call	Visit[1]/ Call[3]	Visit[1]	Call	Visit[1]	Visit[1]	Call
Screening only	Informed consent	X																
Screening only	Demography	X																
Screening only	COVID-19 Disease History[4]	X																
Screening only	Medical history (incl. comorbidities and tobacco use)	X																
Screening only	SARS-CoV-2 diagnostic test (if not previously confirmed)[5]	X																
	Randomization[6]		X															
	Study intervention administration		X															
Assessments	Full physical examination	X[7,8]	X															
Assessments	COVID-19 signs/symptoms review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments	Vital Signs (BP, PR, RR, temperature and oxygen saturation)	X[8]	X[9]	X	X	X	X	X	X	X	X						X	
Assessments	Local injection site tolerability assessment (IM injections only)		X[10]	X[10]	X[10]													
Assessments	12-lead ECG[11]	X[8]	X			X		X						X				
Sample collection	Safety lab assessments	X[8]	X[12]	X[12]		X	X				X							
Sample collection	Pregnancy test[13]	X															X	
Sample collection	Blood sample for PK analysis (Lead-in phase)[14]		X[14]	X	X	X	X		X		X		X	X		X	X	
Sample collection	Blood sample for PK analysis (Expansion phase)[14]		X[14]		X		X		X		X			X		X	X	
Sample collection	Blood sample for anti-drug antibody		X[15]								X			X		X	X	
Sample collection	Nasopharyngeal swab for virology		X[15]	X	X	X	X	X	X	X	X							
Sample collection	Blood sample for Anti-SARS-CoV-2 antibody (serum)		X[15]								X							
	AE review		<========== X ==========>															
	SAE review	X[16]		<========== X ==========>														
	AESI, disease-related events, and concomitant medication review			<========== X ==========>														

Notes

1. Visits other than Screening and Day 1 may take place at home, where local home nursing support is available.
2. Phone calls may be replaced by a visit at investigator's discretion.
3. Week 8/Day 57 must be an in-person visit for the Lead-in phase, but may be a phone call for the Expansion phase.
4. Data on the history of COVID-19 illness prior to enrollment should be collected in the specific eCRF.
5. As per institution diagnostic protocols.
6. All screening procedures must be completed within 1 day prior to dosing. Screening and dosing may take place on the same day.
7. Including height and weight.
8. If screening and dosing occur on the same day: full physical examination, pre-treatment vital signs, and pre-treatment safety lab assessments are only performed once, and the single screening ECG is not required (pre- and post-dose triplicate[11] ECGs are still required).
9. For Lead-in and Expansion phases prior to JSRT recommendation: Record Day 1 vital signs within 1 hour prior to dosing, and at the end of infusion (IV infusion only) then approximately 30 minutes, 1 hour and 2 hours after dosing. For Expansion phase after the 13 May 2021 JSRT review: Record Day 1 vital signs within 1 hour prior to dosing, and at the end of infusion (IV infusion only) then approximately 30 minutes and 1 hour after dosing. For both phases: Vital signs on other days should be performed once daily.
10. For Lead-in and Expansion phases prior to JSRT recommendation: Local injection site tolerability assessment on Day 1 at approximately 1 and 2 hours post-dose and on Days 2 and 3 for all participants. Expansion phase after the 13 May 2021 JSRT review: Local injection site tolerability assessment on Day 1 at approximately 1 hour post-dose, those with severe ISRs on Day 1 need to be assessed in-person at Day 2 *or* 3. All ISRs to be followed by PI to resolution.
11. Day 1: triplicate ECGs prior to dosing and within 30 minutes of end of infusion or post-injection. All other timepoints are single 12-lead ECGs.
12. Day 1 safety labs should be collected pre-dose. Urine for albumin to creatinine ratio should be collected on Day 1 (pre-dose) and on Day 2.
13. Urine or serum pregnancy test, as per local guidelines. See 8.4.7.
14. Day 1, sample collection will occur pre-dose (IM and IV) and at end of infusion (IV only). On other days, samples will be collected once daily.
15. On Day 1, sample collection will occur pre-dose.
16. At screening, only SAEs related to study participation or a GSK product will be reported.
17. If participant withdraws early from the study prior to Week 24, then the W24 visit assessments will be performed as the EW visit. If the participant withdraws early from the study after Week 24, the W36 visit assessments will be performed as the EW visit.

Table 3 Schedule of Activities: Part C

	Study Visit Day ± Visit Window[17]	Screening (Day 0/1)	W1 Day 1	W1 Day 2	W1 Day 3	W1 Day 5	W2 Day 8	W2 Day 11	W2 Day 15 ± 1d	W3 Day 22 ± 1d	W4 Day 29 ± 2d	W6 Day 43 ± 3d	W8 Day 57 ± 4d	W12 Day 85 ± 7d	W16 Day 113 ± 7d	W20 Day 141 ± 7d	W24 Day 169 ± 7d	W36 Day 253 ± 7d
	Site visit[1], home visit[1], or call[2]	Visit	Visit	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Visit[1]	Call	Visit[1]/ Call[3]	Visit[1]	Call	Visit[1]	Visit[1]	Call
Screening only	Informed consent	X																
Screening only	Demography	X																
Screening only	COVID-19 Disease History[4]	X																
Screening only	Medical history (incl. comorbidities and tobacco use)	X																
Screening only	SARS-CoV-2 diagnostic test (if not previously confirmed)[5]	X																
	Randomization[6]		X															
	Study intervention administration		X															
Assessments	Full physical examination	X[7,8]	X															
Assessments	COVID-19 signs/symptoms review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments	Vital Signs (BP, PR, RR, temperature and oxygen saturation)	X[8]	X[9]	X	X	X	X	X	X	X	X						X	
Assessments	Local injection site tolerability assessment (IM injections only)		X[10]	X[10]	X[10]													
Assessments	12-lead ECG[11]	X[8]	X			X		X						X				
Sample collection	Safety lab assessments	X[8]	X[12]	X[12]		X	X				X							
Sample collection	Pregnancy test[13]	X															X	
Sample collection	Blood sample for PK analysis (Lead-in phase)[14]		X[14]	X	X	X	X		X		X		X	X		X	X	
Sample collection	Blood sample for PK analysis (Expansion phase)[14]		X[14]		X		X		X		X			X		X	X	
Sample collection	Blood sample for anti-drug antibody		X[15]								X			X		X	X	
Sample collection	Nasopharyngeal swab for virology		X[15]	X	X	X	X	X	X	X	X							
Sample collection	Blood sample for Anti-SARS-CoV-2 antibody (serum)		X[15]								X							
	AE review		<========== X ==========>															
	SAE review	X[16]		<========== X ==========>														
	AESI, disease-related events, and concomitant medication review			<========== X ==========>														

Notes

1. Visits other than Screening and Day 1 may take place at home, where local home nursing support is available.
2. Phone calls may be replaced by a visit at investigator's discretion.
3. Week 8/Day 57 must be an in-person visit for the Lead-in phase, but may be a phone call for the Expansion phase.
4. Data on the history of COVID-19 illness prior to enrollment should be collected in the specific eCRF.
5. As per institution diagnostic protocols.
6. All screening procedures must be completed within 1 day prior to dosing. Screening and dosing may take place on the same day.
7. Including height and weight.
8. If screening and dosing occur on the same day: full physical examination, pre-treatment vital signs, and pre-treatment safety lab assessments are only performed once, and the single screening ECG is not required (pre- and post-dose triplicate[11] ECGs are still required).
9. For Lead-in and Expansion phases prior to JSRT recommendation: Record Day 1 vital signs within 1 hour prior to dosing and at the end of infusion (IV infusion only) and then approximately 30 minutes and 1 hour after dosing. For Expansion phase if JSRT recommend reduced 30-minutes post-dose monitoring: Record Day 1 vital signs within 1 hour prior to dosing, at the end of infusion (IV infusion only), and approximately 30 minutes after dosing. For both phases: Vital signs on other days should be performed once daily.
10. For Lead-in and Expansion phases prior to JSRT recommendation: Local injection site tolerability assessment on Day 1 at approximately 1 hour post-dose and on Days 2 and 3 for all participants. Expansion phase if JSRT recommend reduced 30-minutes monitoring: Local injection site tolerability assessment on Day 1 at approximately 30 minutes post-dose, those with severe ISRs on Day 1 need to be assessed in-person at Day 2 *or* 3. All ISRs to be followed by PI to resolution.
11. Day 1: triplicate ECGs prior to dosing and within 30 minutes of end of infusion or post-injection. All other timepoints are single 12-lead ECGs.
12. Day 1 safety labs should be collected pre-dose. Urine for albumin to creatinine ratio should be collected on Day 1 (pre-dose) and on Day 2.
13. Urine or serum pregnancy test, as per local guidelines. See 8.4.7.
14. Day 1, sample collection will occur pre-dose (IM and IV) and at end of infusion (IV only). On other days, samples will be collected once daily.
15. On Day 1, sample collection will occur pre-dose.
16. At screening, only SAEs related to study participation or a GSK product will be reported.
17. If participant withdraws early from the study prior to Week 24, then the W24 visit assessments will be performed as the EW visit. If the participant withdraws early from the study after Week 24, the W36 visit assessments will be performed as the EW visit.

2. INTRODUCTION

2.1. Study Rationale

There is an urgent medical need for therapeutics for the treatment of coronavirus disease 2019 (COVID-19). A highly potent neutralizing monoclonal antibody (mAb) given as early treatment in outpatients with mild to moderate disease could prevent the need for hospitalization in patients at high risk of disease progression. Vir Biotechnology, Inc. (Vir) is developing VIR-7831 (also known as GSK4182136, sotrovimab) for the treatment and prophylaxis of COVID-19. VIR-7831 is a human immunoglobulin G (IgG1) monoclonal antibody (mAb) that binds to a highly conserved epitope on the spike protein receptor binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). VIR-7831 has an Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life [Hope, 2020; Ko, 2014].

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

COMET-ICE, is a seamless first-in-human (FIH) Phase II/III study assessing the safety and efficacy of a single 500 mg intravenous dose of VIR-7831 for the early treatment of COVID-19 in non-hospitalized participants at high risk for progression and subsequent hospitalization. Participants were randomized in a 1:1 ratio to VIR-7831 or placebo. COMET-ICE started with a lead-in phase (N=21) in August 2020 to assess safety and tolerability. An Independent Data Monitoring Committee (IDMC) met 23 September 2020 to review unblinded safety data after the 20th participant from the lead-in cohort completed Day 15 (1 participant was withdrawn). There were no deaths or serious adverse events reported up to this IDMC review. The IDMC recommended the study to proceed with the expansion-phase to enroll additional participants across each treatment group (~1300 participants total).

Subsequently, the IDMC met to review available safety and tolerability data on 28 January 2021. At the data cutoff of 22 January 2021, safety data was available from 526 participants (of 532 enrolled) including 405/532 (76%) who were at least 15 days post-dosing. Available data indicate that 99/526 (19%) participants experienced an AE with 10 (2%) participants experiencing an AE related to study treatment. One participant experienced an SAE of respiratory distress with onset 10 days after study drug infusion that led to patient discontinuation from the study follow up. This event occurred on Day 12 and resolved on Day 27, lasting 16 days. In the validated dataset shared with the IDMC, there were 22 SAEs reported, the majority of which represented respiratory progression of COVID-19 disease leading to hospitalization (i.e. disease progression) which is also the primary efficacy endpoint. Of these, one participant of the 526 for whom safety data was available (<1%) experienced an SAE coded to Preferred Term Covid-19, which was later updated to Covid-19 pneumonia, and was considered related. The IDMC recommended the study to continue with no adaptation.

The IDMC subsequently met on 10 March 2021 for a planned interim analysis, with review of data from 583 participants. There was an 85% reduction in the primary endpoint of hospitalization or death in the VIR-7831 arm versus the placebo arm (p=0.002). The IDMC recommended that the study halt enrollment on the basis of overwhelming efficacy [Vir Biotechnology, 2021].

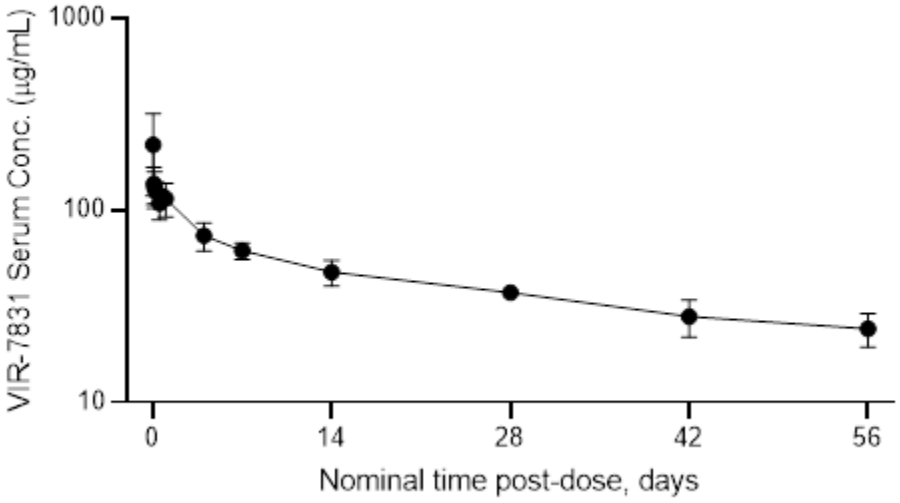
VIR-7831 was also being studied for the treatment of hospitalized participants with COVID-19 in Study 215149, also known as ACTIV-3-TICO, sponsored by the National Institute of Allergy and Infectious Diseases. The ACTIV-3-TICO study is a randomized, blinded, placebo-controlled platform study that allows investigational drugs to be added and dropped during the course of the study. The sub-study evaluating VIR-7831 started in December 2020 and aimed to enroll approximately 500 participants per treatment arm.

A Data and Safety Monitoring Board (DSMB) review for ACTIV-3-TICO to include the VIR-7831 sub-protocol occurred on 25 January 2021. The DSMB reviewed data from 148 participants who had been randomized to VIR-7831 or shared placebo. One potentially life-threatening allergic reaction (anaphylaxis) was reported during infusion in ACTIV-3-TICO in a participant that received VIR-7831. 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 VIR-7831 sub-study should continue as planned.

The DSMB met on 01 March 2021 for a pre-planned safety and efficacy data review. While VIR-7831 met initial pre-specified criteria to continue to the next phase of the ACTIV-3 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, 2021a].

Partial blinded serum PK through Study 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 VIR-7831, based on nominal times are presented in Figure 1 and Table 4, respectively. The mean maximum concentration (C_{max}) of 500 mg VIR-7831 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 AUC is being extrapolated and the observation range for 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 the area under the serum concentration-time curve from zero to infinity (AUC_{inf}) will be reported once sufficient data are available.

Figure 1 Preliminary Mean Concentration vs Time Profile of VIR-7831 in Serum: COMET-ICE Intensive Lead-in Pharmacokinetics



Note: Concentrations are displayed as mean ± standard deviation.

Table 4 Preliminary VIR-7831 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)
%AUCexp, %	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 from zero to infinity; %AUCexp = The extrapolated portion of AUC_{inf}; C_{D29} = observed concentration on Day 29 (28 days post-dose); C_{last} = concentration at last quantifiable timepoint; C_{max} = maximum observed concentration; CL = clearance; $t_{1/2}$ = terminal elimination half-life; T_{last} = time of the last quantifiable concentration; T_{max} = time to reach C_{max}; TBD = to be determined; V_z = apparent volume of distribution during the elimination phase.

Parameters are reported as mean (%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 % Extrapolated.

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.

Partial sparse serum PK through Day 29 from 176 participants in the Expansion phase of COMET-ICE is available to date. PK sampling will continue for 6 months for all participants. The mean serum concentration of VIR-7831 on Day 29 in the Expansion phase of COMET-ICE is 34.6 µg/mL.

Vir partnered with WuXi Biologics to initiate manufacturing activities to enable rapid entry of VIR-7831 into the COMET-ICE study in August 2020. Initially, two manufacturing batches were produced from a pool of cells (non-clonal) stably transfected to express the VIR-7831 sequences (Generation 1 [Gen1]). Additional cGMP drug substance has been produced at WuXi Biologics using a similar manufacturing process but from a clonal Master Cell Bank (MCB) derived from the original pool of transfectants (Generation 2 [Gen2]).

COMET-ICE and ACTIV-3-TICO utilized Gen1 material. Analytical comparability studies evaluating Gen1 drug substance (DS) and drug product (DP) in relation to Gen2 DS and DP have recently been completed. These studies included routine release analysis and extended characterization and were designed and completed in alignment with International Council for Harmonisation (ICH) Q5E guidelines (comparability of biotechnological/biological products subject to changes in their manufacturing process). These confirm a high degree of analytical and bioanalytical comparability between Gen1 and Gen2, thereby supporting the use of Gen2 in clinical studies.

In addition, Gen2 IV material was used in the BLAZE-4 study (NCT04634409), a clinical trial with multiple arms evaluating anti-SARS-CoV-2 mAbs from Eli Lilly and Company. One arm compared the combination of bamlanivimab with VIR-7831 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 February 2021, with no safety concerns identified as of 17 March 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 VIR-7831 500 mg. Co-administration of bamlanivimab and VIR-7831 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 [GlaxoSmithKline plc, 2021b].

Since Gen2 will be the commercial product, Vir is proposing this study to gain clinical experience with Gen2 administered both intravenously (IV) and via IM injection in non-hospitalized patients with mild to moderate COVID-19, a patient population similar to that of COMET-ICE, to complement the analytical and bioanalytical data. This study will evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and viral PD of both IV and IM formulations of VIR-7831 Gen2 (500 mg IV, 500 mg IM, and 250 mg IM) when administered in this early treatment population. Part A of the study will evaluate Gen2 and Gen1 500 mg administered via IV infusion. Part B will evaluate Gen2 500 mg via IV infusion and 500 mg via IM injection. Part C will evaluate Gen2 500 mg via IV infusion and 250 mg via IM injection. Intramuscular injection of VIR-7831 will also be evaluated in the following planned studies:

- A study evaluating efficacy, safety, and tolerability of VIR-7831 IM (250 mg and 500 mg) versus VIR-7831 IV (500 mg) for treatment of mild/moderate COVID-19 in non-hospitalized participants at high risk for disease progression (VIR-7831-5008 [GSK Study 217114] also known as COMET-TAIL)

- Studies evaluating VIR-7831 IM (500 mg) as prophylaxis against SARS-CoV-2 infection.

2.2. Background

A novel beta-coronavirus causing severe pneumonia was first reported in December 2019 in Wuhan, China. Since that time, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread throughout the world. As of 09 May 2021, there have been approximately 157.8 million confirmed cases and >3.2 million deaths globally with approximately 32.7 million cases and 581,659 deaths in the United States [Johns Hopkins COVID Dashboard, 2021].

The spectrum of symptomatic COVID-19 disease ranges from mild disease without pneumonia to critical disease requiring hospitalization in an intensive care unit (ICU). A comprehensive report from the Chinese Center for Disease Prevention and Control which included nearly 45,000 confirmed cases estimated that the vast majority of patients, 81%, were classified as having mild disease with no or mild pneumonia [Wu, 2020]. In the same study, 14% were classified as having severe disease, and 5% as having critical disease. Risk factors for severe disease and/or death include older age and certain comorbidities such as cardiovascular disease, diabetes mellitus, obesity, respiratory disease (e.g., chronic obstructive pulmonary disease), tobacco use, and chronic kidney disease. The current estimated infection fatality rate increases exponentially with age, from 0.004% in individuals younger than 35 to 28.3% in the population 85 years and older [Levin, 2020].

In the United States, data on the proportion of patients with symptomatic disease requiring hospitalization have ranged from 21% overall to as high as 40% in those with at least one pre-existing health condition [CDC, 2020]. The median time for COVID-19 related hospital admission has been reported to be 7 to 11 days and the median time to clinical deterioration, 9 to 12 days [Huang, 2020; Zheng, 2020; Zhou, 2020].

Complications are common among hospitalized patients, including respiratory failure with acute respiratory distress syndrome (ARDS); cardiomyopathy; thromboembolic disease with pulmonary embolism and/or stroke; shock; and multiorgan dysfunction [Wang, 2020; Klok, 2020; Arentz, 2020]. Multisystem inflammatory syndrome (MIS), a hyperinflammatory syndrome with involvement of multiple organ systems and often requiring ICU-level support, has also been recently described in adults [Morris, 2020]. While long-term complications of COVID-19 have been described mostly in the hospitalized population, there are increasing data demonstrating significant long-term sequelae in patients with mild to moderate disease not requiring hospitalization, including long-term disability and prolonged duration of illness before a return to baseline functioning [Tenforde, 2020].

Monoclonal antibodies directed against SARS-CoV-2 have the potential to both be used for 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 in particular 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 November 2020 for casirivimab and imdevimab (to be administered together) and on 09 February 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 [FDA News Release, 2020; FDA News Release, 2021]. 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, 2020; FDA News Release, 2020; FDA News Release, 2021].

Given that these mAbs are currently indicated for intravenous administration, a mAb that is able to 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 is able to be administered via IM injection would be able to 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. In addition, being able to provide an efficacious 250 mg IM dose of mAb via deltoid injection would allow for ease of administration across a considerably larger number of settings for high-risk patients, including pharmacies. Lastly, a shorter required duration for monitoring post-administration (e.g., 30 minutes) would improve the ease of delivery for clinics, pharmacies, and other sites where non-hospitalized patients would be able to receive treatment.

Given the high degree of analytical and bioanalytical comparability between Gen1 and Gen2 material, a formal clinical comparability study will not be conducted. However, Vir proposes to gain clinical experience with Gen2 material across multiple clinical studies, including this study in non-hospitalized patients with mild to moderate COVID-19. Gen2 material is also anticipated to be used in future planned studies of VIR-7831 in various patient populations (i.e., hospitalized patients, patients requiring prophylaxis).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of VIR-7831 may be found in the IB.

2.3.1. Risk Assessment

All the potential clinical risks of VIR-7831 are based on theoretical and known concerns associated with the mAbs class of therapeutics in general. The potential risk monitoring and mitigation strategy for the administration of VIR-7831 in this protocol is outlined below:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: VIR-7831		
Infusion-related reactions including serious hypersensitivity reactions (HSR)	While VIR-7831 is a human immunoglobulin G1 (IgG1) mAb, infusion-related reactions (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 in Part A of the study will be monitored every 15 minutes over the 1-hour IV infusion and at 1, 2, 6, and 8 hours in the post-infusion period. Vital signs in the Lead-in phase of Part B of the study will be monitored before and at the end of the 15 minute IV infusion, and at 30 minutes, 1 hour, and 2 hours post-infusion. Vital signs in the Lead-in phase of Part C of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		the study will be monitored before and at the end of the 15 minute IV infusion, and at 30 minutes and 1 hour post-infusion. • IRRs are categorized as adverse events of special interest (AESI). • The Joint Safety Review Team (JSRT) will review blinded safety data of this study at regular intervals to determine if a significant safety concern for severe hypersensitivity reaction is identified. **Mitigation**: • General guidance on management of hypersensitivity reactions is provided in Section 8.5.9.1 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. • Investigators will be instructed to discontinue intravenous (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. • 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 & resuscitation procedures & emergency care kit on hand during the infusion & post therapy observation periods.
Injection Site Reaction (ISR)	VIR-7831 will be administered via intramuscular injection. A similar human immunoglobulin G1 (IgG1) mAb specific to influenza A (VIR-2482) has been studied in a recent Phase I trial (NCT04033406). 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 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 subjects discontinued due to an AE.	Injection site reactions will be monitored very closely in the Lead-in phase of Part B of the study in 20 participants (N=10 in the Gen2 VIR-7831 IV arm; N=10 in the Gen2 VIR-7831 IM arm) for 2 hours and for 1 hour in the Lead-in phase of Part C (N=10 in the Gen2 VIR-7831 IV arm; N=10 in the Gen2 VIR-7831 IM arm). Monitoring will also be performed for systemic symptoms post-dosing (e.g., fever, chills, malaise). Local injection site tolerability assessment data was evaluated by the JSRT prior to decreasing the monitoring time to 1 hour for the Expansion phase of Part B and will be assessed by the JSRT prior to decreasing the monitoring time to 30 minutes for Part C.
Immunogenicity	While VIR-7831 is a human IgG1 mAb, the development of anti-drug antibodies (ADA) that have the potential to impact safety and/or efficacy are a potential general risk associated with the mAb class of therapeutics.	**Monitoring:** This study will include participant follow-up for a period of 24 weeks to assess for the potential of immunogenicity (measurement of ADA) as well as if ADA is potentially causally associated with specific safety concerns.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Antibody-dependent enhancement (ADE) due to sub-neutralizing levels of VIR-7831 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 36 weeks to assess for the potential of enhanced disease in the context of waning VIR-7831 levels. Assessments of the overall incidence of COVID-19 re-infection as well as the severity of disease will be performed by the JSRT to assess for rates of re-infection or severe disease above what is clinically expected.
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].	**Monitoring:** • In this study, periodic review of AEs which are potential clinical signs and symptoms of COVID-19, clinical chemistry, other AEs, end-organ disease, cardiac assessments, and histopathological diagnoses (as available per routine care) observed through to Week 36 will be performed by the Joint Safety Review Team (JSRT) at regular intervals to identify potential cases of immune complex disease (e.g., worsening of COVID-19-related end-organ complications and/or greater than

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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]. VIR-7831 shows potent binding as well as neutralization of pseudovirus and live virus *in vitro*, thus this risk is deemed to be low. VIR-7831 Clinical experience: A total of 21 subjects were enrolled in the Lead-In phase of the COMET-ICE study. Patients were randomized 1:1 to VIR-7831 or placebo. As of the Day 15 follow-up (data cut 28 September 2020), no safety signals have been observed, and no subjects died or discontinued the study due to AEs to date. No evidence of ADE with SARS-CoV-2 per IDMC criteria has been observed. On 30 September 2020, the IDMC recommended initiation of the Expansion study phase based on safety assessment	expected incidence of end-organ complications [Chen, 2020]). • Additional monitoring in the event a participant develops signs or symptoms of cardiac complications (See Section 8.5.7). • Assessments of the overall duration and severity of COVID-19 will be performed by the JSRT to assess for greater than expected duration and/or severity of COVID-19 disease

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of unblinded Lead-In data. Enrollment in the Expansion phase is ongoing. Subsequently, the IDMC met to review available safety and tolerability data on 28 January 2021. At the data cutoff of 22 January 2021, safety data was available from 526 participants (of 532 enrolled) including 405/532 (76%) who were at least 15 days post-dosing. Available data indicate that 99/526 (19%) participants experienced an AE with 10 (2%) participants experiencing an AE related to study treatment. One participant experienced an SAE of respiratory distress with onset 10 days after study drug infusion that led to patient discontinuation from the study follow up. This event occurred on Day 12 and resolved on Day 27, lasting 16 days. In the validated dataset shared with the IDMC, there were 22 SAEs reported, the majority of which represented respiratory progression of COVID-19 disease leading to hospitalization (i.e. disease progression) which is also the primary efficacy endpoint. Of these, one participant of the 526 for whom safety data was available (<1%) experienced an SAE coded to Preferred Term Covid-19, which was later updated to Covid-19 pneumonia, and was considered related. The IDMC recommended the study to continue with no adaptation. The IDMC subsequently met on 10 March 2021 for a planned interim analysis, with review of data from 583 participants. No serious safety concerns were identified, and the IDMC recommended to halt enrollment based on overwhelming efficacy.	

2.3.2. Benefit Assessment

There is a biologic rationale to support the use of VIR-7831, an antiviral mAb, in the early treatment of COVID-19 to prevent disease progression. The mainstay of outpatient treatment of COVID-19 is supportive care and monitoring. Recent EUAs were also granted for the mAbs bamlanivimab/etesevimab in combination and casirivimab/imdevimab in combination for the treatment of mild to moderate COVID-19 in adults and pediatric patients (≥12 years of age and weighing ≥40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization FDA News Release, 2020; FDA News Release, 2021. Specific treatments for COVID-19 in the non-hospitalized patient population remain limited.

VIR-7831 has been demonstrated *in vitro* to be a highly potent human IgG1 neutralizing SARS-CoV-2 antibody with additional antibody effector functions. The non-clinical pharmacology, pharmacokinetics and toxicology results support the evaluation of VIR-7831 in humans for the treatment of COVID-19 infection. VIR-7831 has the potential to be an effective therapeutic in mild to critically ill patients with COVID-19 infection.

The study population to be enrolled in this study are non-hospitalized patients with mild to moderate COVID-19, a population that has a high unmet medical need. The safety and tolerability of Gen1 material has been assessed in 21 patients in the lead-in phase of the COMET-ICE study in non-hospitalized patients with mild to moderate COVID-19 at high risk for progression, with a safe to proceed recommendation issued by the IDMC after meeting 23 September 2020 following Day 15 data review (data cut off: 28 September 2020). Subsequently, the IDMC met to review available safety and tolerability data on 28 January 2021. At the data cutoff of 22 January 2021, safety data was available from 526 participants (of 532 enrolled) including 405/532 (76%) who were at least 15 days post-dosing. The IDMC recommended the study to continue with no adaptation.

Importantly, the IDMC subsequently met on 10 March 2021 for a planned interim analysis, with review of data from 583 participants. There was an 85% reduction in the primary endpoint of hospitalization or death in the VIR-7831 arm versus the placebo arm (p-value=0.002). The IDMC recommended that the study halt enrollment on the basis of overwhelming efficacy [Vir Biotechnology, 2021].

VIR-7831 was also being studied for the treatment of hospitalized participants with COVID-19 in Study 215149, also known as ACTIV-3-TICO, sponsored by the National Institute of Allergy and Infectious Diseases. The DSMB reviewed ACTIV-3-TICO including the VIR-7831 sub-protocol on 25 January 2021. The DSMB reviewed data including a potentially life-threatening allergic reaction (anaphylaxis) that was reported during infusion of VIR-7831 in ACTIV-3-TICO. The DSMB recommended the VIR-7831 sub-study should continue as planned.

The DSMB subsequently met on 01 March 2021 for a pre-planned safety and efficacy data review. While VIR-7831 met initial pre-specified criteria to continue to the next phase of the ACTIV-3 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, 2021a].

A high degree of analytical and bioanalytical comparability has been shown between Gen1 and Gen2. VIR-7831 (Gen1 or Gen2) may or may not improve the time to clinical response or overall clinical outcome in an individual participant with mild to moderate COVID-19 who participates in this study. However, there is potential benefit from their participation in this study resulting from their data allowing evaluation of VIR-7831 (both Gen1 and Gen2 material) as a potential treatment for this new disease.

2.3.3. Overall Benefit: Risk Conclusion

The overall benefit-risk assessment takes into account the potential benefit of VIR-7831 treatment through the potential ability to suppress viral replication and clear infected cells.

No clinical studies of VIR-7831 have been completed to date. There is prior clinical experience with VIR-7831 in the setting of the early treatment of COVID-19 (COMET-ICE 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 March 2021, there have been no safety concerns identified in the BLAZE-4 study. In the ACTIV-3-TICO study, one case of anaphylaxis was reported during infusion of VIR-7831 which resolved with treatment.

VIR-7831 has the potential to be an effective therapeutic in mild to critically ill patients with COVID-19. This benefit has been demonstrated in the interim analysis of the COMET-ICE study of participants with mild to moderate COVID-19 at high risk of disease progression, a similar non-hospitalized population as for the COMET-PEAK study [Vir Biotechnology, 2021]. Human-derived mAbs with similar Fc modifications as VIR-7831, have a well-established safety profile [Gaudinski, 2018]. Considering the measures taken to minimize risk to participants in this study, including close monitoring for IRRs in Part A of the study and for ISRs and IRRs in the Lead-in phase of Parts B and C of the study (Gen2 IV and IM), and the limited disease directed therapeutic options for non-hospitalized patients with mild to moderate COVID-19, the overall benefit-risk assessment of this study is considered favorable based on the available data.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Safety (Part A) To evaluate the safety and tolerability profile of intravenous (IV) VIR-7831 Gen2 and IV Gen1	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29

Objectives	Endpoints
	• 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 disease progression events (not classified as AEs) through Day 29
Pharmacodynamics (Part B) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via intramuscular (IM) injection (500 mg) in the upper respiratory tract	• Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUC_{D1-8}) in nasopharyngeal swab samples
Pharmacodynamics (Part C) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via IM injection (250 mg) in the upper respiratory tract	• Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUC_{D1-8}) in nasopharyngeal swab samples
Secondary	
Safety (Part A) To evaluate the safety and tolerability profile of IV VIR-7831 Gen2 and IV Gen1	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 36 • Occurrence of AESIs through Week 36 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 36
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, 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

Objectives	Endpoints
	• Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29 • Occurrence of disease progression events (not classified as AEs) through Day 29
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, through End of Study (EOS)	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 36 • Occurrence of AESIs through Week 36 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 36
Virology (Part A) To characterize the effect of VIR-7831 Gen2 IV and Gen1 IV on the viral shedding profile in the upper respiratory tract	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from saliva and nasal mid-turbinate swabs samples
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and Gen2 IM on the viral shedding profile in the upper respiratory tract	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from nasopharyngeal (NP) swab samples • Proportion of participants with undetectable viral load at all visits through Day 29 of the study as measured by qRT-PCR from NP swab samples • Mean area under the curve of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 5 (AUC_{D1-5}) and Day 1 to 11 (AUC_{D1-11})
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and IM on viral load clearance in the upper respiratory tract	• Proportion of individuals with a persistently high viral load at Day 8 as assessed via qRT-PCR in NP swab samples (see Section 8.3)
Pharmacokinetics (Part A, Part B, and Part C)	• Serum PK of VIR-7831

Objectives	Endpoints
To assess the pharmacokinetics (PK) of VIR-7831 Gen2 IV and IM and Gen1 IV in serum	
Exploratory	
Resistance (Part A, Part B, and Part C) To monitor the presence at Baseline and the emergence of SARS-CoV-2 resistant mutants against VIR-7831	• Presence at Baseline and emergence of SARS-CoV-2 viral resistance mutants
Immunogenicity (Part A, Part B , and Part C) To assess the immunogenicity of VIR-7831 Gen2 IV and IM and Gen1 IV	• Incidence and titers (if applicable) of serum anti-drug antibodies (ADA) to VIR-7831
Immunology (Part A, Part B and Part C) To assess the effect of VIR-7831 Gen2 IV and IM and Gen1 IV on immune response	• Incidence and titers (if applicable) of anti-nucleocapsid (anti-N), anti-spike (anti-S) and anti-receptor binding domain (anti-RBD) SARS-CoV-2 antibodies at baseline • Incidence and titers (if applicable) of anti-N SARS-CoV-2 antibodies at Day 29

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, multi-center, parallel group phase II trial of VIR-7831, a monoclonal antibody (mAb) against SARS-CoV-2 for the prevention of progression of mild to moderate COVID-19 in non-hospitalized patients. This study will be conducted in three Parts (Parts A, B, and C).

Part A:

Participants with early mild to moderate COVID-19 will be randomized 3:1 to receive a single, 500 mg intravenous infusion of either Gen2 or Gen1 study material. Safety, tolerability, virology, immunogenicity, and PK will be evaluated. Part A is double-blinded.

- Screening assessments will be performed within 1 day before the start of infusion. Eligible participants will be treated in a blinded manner with a single IV dose on Day 1 and followed up to 36 weeks. Participants will be monitored for

approximately 9 hours on Day 1 for safety assessments and intensive PK sampling.

Part B:
Participants with early mild to moderate COVID-19 will be randomized 1:1 to receive a 500 mg dose of Gen2 study material by IV infusion or IM injection. In Part B, viral load pharmacodynamics (PD) as assessed via upper respiratory samples, safety, tolerability, immunogenicity, and PK will be evaluated. Part B is open-label. Part B will include a Lead-in phase with frequent assessments for injection site reactions (ISRs) and safety, along with intensive PK sampling.

Screening assessments will be performed within 1 day before the start of infusion or IM injection. Lead-in phase safety data (e.g., ISRs) through Day 3 for 20 participants (10 receiving IV Gen2 and 10 receiving IM Gen2) will be reviewed in an unblinded manner by the JSRT. In the Lead-in phase, participants will be monitored for a period of 2 hours post-injection or post-infusion for ISRs and IRRs. Once participants for the Lead-in phase (n=20) have been recruited, new participants will be enrolled into the Expansion phase. However, the post-dose monitoring period for the Expansion phase will remain at 2 hours until a recommendation to shorten monitoring to 1 hour is issued by the JSRT, based on a review of unblinded aggregate safety data through Day 3 of the Lead-in phase, including ISRs and IRRs.

A JSRT review on 13 May 2021 identified no serious safety concerns on review of 66 participants enrolled in Part B (all of the Lead-in participants and some Expansion phase participants). Based on this safety review, the JSRT agreed with the proposal to reduce the post-dose monitoring time on Day 1 from 2 hours to 1 hour for Part B of the study.

Part C:
Participants with early mild to moderate COVID-19 will be randomized 1:1 to receive a 500 mg dose of Gen2 study material by IV infusion or a 250 mg dose of Gen2 study material by IM injection. Participants will be stratified by prior exposure to an authorized or approved SARS-CoV-2 vaccine. Prior exposure includes any of the following scenarios: one dose of a one-dose series; first dose of a two-dose series; or second dose of a two-dose series.

In Part C, viral load PD as assessed via upper respiratory samples, safety, tolerability, immunogenicity, and PK will be evaluated. Part C is open label. Part C will include a Lead-in phase with assessments for safety to inform the JSRT review of data through Day 3 and subsequent decision on whether the Day 1 monitoring time can be decreased (from 1 hour to 30 minutes), along with intensive PK sampling.

Screening assessments will be performed within 1 day before the start of infusion or IM injection. Lead-in phase safety data (e.g., ISRs) through Day 3 for 20 participants (10 receiving 500 mg IV Gen2 and 10 receiving 250 mg IM Gen2) will be reviewed in an unblinded manner by the JSRT. In the Lead-in phase, participants will be monitored for a period of 1 hour post-injection or post-infusion for ISRs and IRRs. Once participants for the Lead-in phase (n=20) have been recruited, new participants will be enrolled into the Expansion phase. However, the post-dose monitoring period for the Expansion phase will

remain at 1 hour until a recommendation to shorten monitoring to 30 minutes is issued by the JSRT, based on a review of unblinded aggregate safety data through Day 3 of the Lead-in phase, including ISRs and IRRs.

4.2. Scientific Rationale for Study Design

Vir has completed analytical comparability testing for the changes from the WuXi 2k Gen1 DS and DP to the WuXi 2k Gen2 DS and DP. A high degree of analytical and bioanalytical comparability has been demonstrated between Gen1 and Gen2, supporting the use of Gen2 in clinical trials. While a dedicated clinical comparability study is not planned, because Gen2 will be the commercial product, Vir proposes to gain clinical experience with Gen2 material across multiple clinical studies, including in non-hospitalized patients with mild to moderate COVID-19. The study will include non-hospitalized patients with mild to moderate SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests. A single dose level of Gen1 or Gen2 material designed to provide potential therapeutic benefit will be studied and will be delivered via IV infusion (Gen1 and Gen2) or IM injection (Gen2). Participants will receive the infusion or IM injection in a clinic/study unit where they will be monitored closely for adverse events in the post-infusion or post-injection period.

Subsequent visits for study activities and clinical monitoring will be conducted via home nursing (Part B and Part C only) or clinic visits (except for Week 16 for Part A; Weeks 6 and 16 for the Part B and Part C Lead-in phases; and Weeks 6, 8, 16, and 36 for the Part B and Part C Expansion phases, which will be conducted via phone call). A double-blind design as implemented for Part A is a standard methodology for randomized, controlled studies to minimize bias. A Gen1 study arm is included to maintain blinding of Gen1 versus Gen2 VIR-7831 study material receipt during the conduct of the study. This blinding will minimize bias that may occur during study assessments, including during evaluation of AEs and disease-related safety outcomes. Given that there has been substantial previous Gen1 clinical experience in COMET-ICE, a randomization ratio of 3:1 for Gen2 to Gen1 was selected to increase the number of participants that will receive Gen2 study material. There is no placebo in this study because the primary aim is to evaluate safety and tolerability of Gen2 material.

Parts B and C of the study will be open-label, as administering placebo IV infusion to participants receiving Gen2 IM injection or placebo IM injection to participants receiving Gen2 IV infusion would unduly impose excess risk from requiring an additional mode of delivery of placebo. In addition, it may be difficult to appropriately attribute an AE or SAE that occurs during study drug administration to VIR-7831 or placebo if participants receive both active and placebo agents at the same visit. Given the open-label design, investigators, site study staff, and participants will not be blinded. The central study team and the JSRT will also be unblinded as some adverse events of special interest (AESIs) are specific to route of administration, i.e., injection site reactions for IM administration and infusion-related reactions for IV administration, and maintaining blinding in this circumstance would be very difficult. Differences in study assessments (e.g., timing) for IM versus IV administration, and other logistical considerations, also support the central team and JSRT remaining unblinded. The objective nature of the primary endpoint (virologic PD) further supports the central team and JSRT remaining unblinded.

Blinded safety data will be reviewed regularly by the JSRT through Week 36 for Part A of the study. For Parts B and Part C of the study, the JSRT will be unblinded, and data will be reviewed through Week 36 according to the Treatment-Sensitive Data Plan for Open-Label Randomized Study. There will be no routine in-stream review of aggregated safety data by treatment arm at any JSRT meeting other than at the two post-Day 3 JSRT meetings (one for Part B and one for Part C) that will determine if the monitoring time may be reduced. Additionally, any sharing of potential safety signals will reflect pooled data that is not separated by treatment arm. The Safety team may need to review single unblinded case reports to support regulatory reporting obligations. All participants will receive standard of care for COVID-19 disease during this study, including admission to a hospital if deemed necessary by the responsible investigator.

4.3. Justification for Dose

The single 500 mg IV dose of VIR-7831 to be evaluated in Parts A, B and C was selected based on extensive nonclinical data and expected human PK extrapolated from cynomolgus monkeys. This IV dose is currently being evaluated in ongoing clinical trials COMET-ICE (NCT04545060), ACTIV-3-TICO (NCT04501978) and BLAZE-4 (NCT04634409), with approximately 1550 participants randomized to either VIR-7831 (500 mg dose) or placebo to date.

The IM doses to be evaluated in Part B (500 mg IM) and Part C (250 mg IM) of this study were selected based on in vitro neutralization data, in vitro resistance data, and simulated IM PK based on preliminary IV PK from the 500 mg dose being evaluated in ongoing clinical studies (COMET-ICE, ACTIV-3-TICO, BLAZE-4). VIR-7831 neutralized 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 VIR-7831 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 VIR-7831. 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 VIR-7831 in the early treatment of COVID-19 (COMET-ICE; NCT04545060), the mean Day 29 serum concentration of VIR-7831 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 VIR-7831 is approximately 47 days.

Intramuscular doses of 250 mg and 500 mg were selected to ensure that the VIR-7831 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 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 intramuscular administration, IM doses of 250 mg and 500 mg are expected to maintain serum levels at or above 5x and 10x lung tissue adjusted EC_{90} through the Day 29 primary endpoint, respectively.

Prior clinical experience with a 500 mg IV dose of VIR-7831 has been gained in the setting of the early treatment of COVID-19 (COMET-ICE 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. 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 VIR-7831 compared to placebo [Vir Biotechnology, 2021]. In ACTIV-3-TICO, one case of anaphylaxis was reported during infusion of VIR-7831 which resolved with treatment. In the BLAZE-4 study, there have been no safety concerns identified as of 17 March 2021.

4.4. End of Study Definition

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 A, Part B, or Part C) through to Week 36 follow up. The end of the study is defined as the date of the last contact of the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Part A: Participant must be aged 18 years or older at the time of obtaining informed consent.

   Part B and C: Participant must be aged ≥18 years to <70 years at the time of obtaining informed consent. The additional age restriction of <70 years for Part B and C is for logistical purposes such that this study and the COMET-TAIL study (a study administering VIR-7831 via IM injection for which planning is currently ongoing), which are enrolling similar populations (non-hospitalized patients with mild to moderate COVID-19), can utilize many of the same sites for participant enrollment. The COMET-TAIL study, which requires that a participant is at high risk for progression to severe disease and/or ≥55 years of age, will be enriching enrollment for participants ≥70 years of age or older.

   Note: For participants at Sites in South Korea refer to inclusion criteria 6.

Type of Participant and Disease Characteristics

2. Participants who have a positive SARS-CoV-2 test result (by any validated test e.g. RT-PCR on any respiratory type) ≤7 days prior to enrollment
   AND
   Oxygen saturation ≥94% on room air
   AND
   Have COVID-19 defined by one or more of the following symptoms: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhea, shortness of breath on exertion
   AND
   ≤7 days from onset of symptoms

Sex and Contraceptive/Barrier Requirements

3. No gender restrictions

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

   A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention. See Section 8.4.7 Pregnancy Testing of the protocol.

   – If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

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

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
   OR
   If participants are not capable of giving written informed consent, alternative consent procedures will be followed as described in Section 10.1.3.

Other Inclusion Criteria

6. For South Korea only: Age ≥19 years of age at the time of obtaining informed consent.

5.2. Exclusion Criteria

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

Medical Conditions

1. Currently hospitalized or judged by the investigator as likely to require hospitalization in the next 24 hours.

   Note: For Participants at Sites in South Korea refer to Exclusion Criteria 16.

2. Symptoms consistent with severe COVID-19 as defined by shortness of breath at rest or respiratory distress or requiring supplemental oxygen.

3. Participants who, in the judgement of the investigator are likely to die in the next 7 days.

4. Severely immunocompromised participants including but not limited to cancer patients receiving immunosuppressive chemotherapy or immunotherapy, those with a solid organ transplant or allogeneic stem cell transplant within the last 3 months, any history of heart or lung transplant or high dose long-term systemic corticosteroids (equivalent to ≥20 mg a day of prednisone or the systemic equivalent for over 2 weeks).

5. Known hypersensitivity to any constituent present in the investigational product.

6. Previous anaphylaxis or hypersensitivity to a monoclonal antibody.

7. For Part B and Part C of the study – Participant has any condition that would prohibit receipt of intramuscular injections in the investigator's opinion, such as coagulation disorder, bleeding diathesis, or thrombocytopenia.

Prior/ Concurrent Clinical Study Experience

8. 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.

9. Enrollment in any trial of an investigational vaccine for SARS-CoV-2.

Other Exclusions

10. The following exclusions related to vaccination are applicable:

    a. Part A and Part B only: Prior receipt of a SARS-CoV-2 vaccine at any time. Vaccination with an authorized or approved SARS-CoV-2 vaccine will not be allowed for 90 days after dosing.

       NOTE FOR PART C: Previous receipt of an authorized or approved SARS-CoV-2 vaccine is NOT an exclusion criteria.

    b. Part A, Part B, and Part C: Receipt of any vaccine within 48 hours prior to enrollment. Vaccination will not be allowed for 90 days after dosing.

11. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.

12. Participants who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol through Day 29.

13. For Germany only: Participants of legal age who are incapable of comprehending the nature, significance and implications of the clinical trial according to §41 paragraph 3 no. 3, according to German Medicinal Products Act (AMG).

14. For Germany only: Participants who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities, according to §40 paragraph 1 sentence 3 no. 4, German Medicinal Products Act (AMG).

15. For Germany only: Participants must not be in a dependent relationship with the site, investigator or sponsor, according to §40 paragraph 1 sentence 3 no. 3 letter b) and c), German Medicinal Products Act (AMG).

16. For South Korea only: Patients with mild to moderate COVID-19 who are hospitalized purely for public health/quarantine purposes in South Korea are not excluded.

5.3. Lifestyle Considerations

Lifestyle considerations are not applicable to this study.

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. Re-screening will be permitted once for each subject during study conduct.

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

Table 5 Overview of Study Intervention

ARM Name	**VIR-7831 Gen1 IV (Part A only)**	**VIR-7831 Gen2 IV (Parts A, B, and C)**	**VIR-7831 Gen2 IM (Part B only)**	**VIR-7831 Gen2 IM (Part C only)**
Intervention Name	VIR-7831 Gen1	VIR-7831 Gen2	VIR-7831 Gen2	VIR-7831 Gen2
Type	Biologic	Biologic	Biologic	Biologic
Dose Formulation	Solution in single use vial (25 mg/mL)	Solution in single use vial (62.5 mg/mL)	Solution in single use vial (62.5 mg/mL)	Solution in single use vial (62.5 mg/mL)
Unit Dose Strength(s)	250 mg Dilution will be with normal saline to achieve equal volume for administration	500 mg Dilution will be with normal saline to achieve equal volume for administration	500 mg	500 mg
Dosage Level(s)	500 mg	500 mg	500 mg	250 mg
Route of Administration	IV infusion	IV infusion	IM injection	IM injection

ARM Name	**VIR-7831 Gen1 IV (Part A only)**	**VIR-7831 Gen2 IV (Parts A, B, and C)**	**VIR-7831 Gen2 IM (Part B only)**	**VIR-7831 Gen2 IM (Part C only)**
Duration of Infusion	1 hour	Part A: 1 hour Parts B and C: 15 minutes	Not applicable	Not applicable
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	VIR-7831 Gen1 will be provided centrally by the sponsor/ designee	VIR-7831 Gen2 will be provided centrally by the sponsor/ designee	VIR-7831 Gen2 will be provided centrally by the sponsor/ designee	VIR-7831 Gen2 will be provided centrally by the sponsor/ designee
Packaging and Labeling	VIR-7831 Gen1 study intervention will be provided in a single-use vial and labeled as required per country requirement.	VIR-7831 Gen2 study intervention will be provided in a single-use vial and labeled as required per country requirement.	VIR-7831 Gen2 study intervention will be provided in a single-use vial and labeled as required per country requirement.	VIR-7831 Gen2 study intervention will be provided in a single-use vial and labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	VIR-7831, GSK4182136, sotrovimab Gen1	VIR-7831, GSK4182136, sotrovimab Gen2	VIR-7831, GSK4182136, sotrovimab Gen2	VIR-7831, GSK4182136, sotrovimab Gen2

In Part A of the study, IV infusion of Gen1 and Gen2 VIR-7831 study material will be administered over a 1-hour period. The COMET-ICE and ACTIV-3-TICO studies administered Gen1 VIR-7831 over a 1-hour period. However, in Part B and C of the study, IV infusion of Gen2 VIR-7831 study material will be administered over 15 minutes, in part to reflect what is expected for the commercial product infusion time. Previous experience for a shorter time of infusion has been gained from the BLAZE-4 study, where no serious infusion-related reactions were noted with a 30-minute infusion time.

In Part B of the study, the 500 mg IM injection will be performed as two 4 mL injections, one in each dorsogluteal muscle.

In Part C of the study, the 250 mg IM dose will be given either as a single 250 mg (4 mL) injection in the dorsogluteal muscle or as two 2 mL injections, one in each deltoid muscle.

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 must receive study intervention and only authorized site staff must 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.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or Sponsor study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

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.

Part A:

Participants will be randomized in a 3:1 ratio to receive an IV infusion of VIR-7831 Gen2 or Gen1 material. In Part A of the study, investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, the study pharmacist will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

For Part A of the study, the IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The

date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded 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 (GSK's) Pharma Safety 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.

Part B:

Participants will be randomized in a 1:1 ratio to receive VIR-7831 Gen2 material by IV infusion or IM injection. As noted in Section 4.2, Part B will be open-label; therefore, no blinding is required.

Part C:

Participants will be randomized in a 1:1 ratio to receive a VIR-7831 Gen2 500 mg IV infusion or 250 mg IM injection. As noted in Section 4.2, Part C will be open-label; therefore, no blinding is required.

Participants will be stratified based on their prior exposure to an approved or authorized SARS-CoV-2 vaccine.

6.4. Study Intervention Compliance

Participants will receive VIR-7831 Gen1 or Gen2 directly from the investigator or designee, under medical supervision. The date and start and stop times of the IV dose and the date and administration time of the IM dose 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

Since this is a single dose study, dose modifications are not applicable. See Section 7.1 for instructions to discontinue study treatment for safety reasons.

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

COVID-19 is an acute illness and participants are not expected to need continued access to VIR-7831 after the end of the study.

6.7. Treatment of Overdose

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

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

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the case report form (CRF).

6.8. Concomitant Therapy

Any vaccine or medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the electronic case report form (eCRF), 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.

6.8.1. Medication Not Permitted During the Study

Given accumulating evidence around the risks associated with the use of hydroxychloroquine and chloroquine and absence of defined benefit, these will NOT be considered standard of care, and are prohibited over the course of the study with the exception of patients with rheumatoid arthritis or systemic lupus erythematosus who are on hydroxychloroquine as a maintenance medication.

Receipt of convalescent plasma from a recovered COVID-19 patient, anti-SARS-CoV-2 mAb, or intravenous immunoglobulin (IVIG) is also not permitted during the study.

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.

6.8.2. Permitted Concomitant Medication

All medication that the participant is receiving as local, established standard of care for acute COVID-19 is permitted.

Receipt of any authorized or approved SARS-CoV-2 vaccine is permitted following 90 days post-dosing for participants in any Part of the study (Part A, B, or C).

For participants in Part C of the study who have not received a SARS-CoV-2 vaccine prior to enrollment, receipt of the first dose of approved SARS-CoV-2 vaccine is permitted following 90 days post-dosing. For those participants who entered Part C of the study following receipt of the first dose of a two-dose vaccine series, the second dose will also be 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.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

For IV administration, a participant will be permanently discontinued from completion of drug infusion if they experience a Grade 3 or 4 IRR (for example, life-threatening, infusion-related reactions including severe allergic or hypersensitivity reactions 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. See the Schedule of Activities in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

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).

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, at the request of their legally authorized representative (LAR) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

- At the time of withdrawal from the study, if possible, an early withdrawal (EW) visit should be conducted, as shown in the Schedule of Activities (Section 1.3). Participants may be contacted by phone. See Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent or the LAR requests that the participant is withdrawn for disclosure of future information, the sponsor/designee may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, he/she or the LAR may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Refer to Section 10.7.1 for additional Germany-specific information regarding participant discontinuation or withdrawal from the study.

7.3. Lost to Follow Up

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

The following actions must be taken if a participant fails to complete a follow-up assessment.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment.

- Study procedures and their timing are summarized in Section 1.3 (Schedule of Activities).

- As most of the follow-up visits include blood collections as noted in the Schedule of Activities, these follow-up assessments may be performed as a home nursing visit (Part B and C) or at the clinic. The Week 16 and Week 36 follow-up visits will be conducted via a site phone call for Part A. For the Part B and Part C Lead-in phases, the Week 6, Week 16, and Week 36 follow-up visits will be conducted via a site phone call. For the Part B and Part C Expansion phases, the Week 6, Week 8, Week 16, and Week 36 follow-up visits will be conducted via a site phone call. Site phone calls may be replaced with a home nursing visit (Part B or Part C) or a clinic visit at the discretion of the investigator.
- 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 Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the Schedule of Activities.
- PK or ADA analysis results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Validated and secure electronic access will be granted to Clinical Research Associates to review the participants' electronic records to verify that the information in the records matches the information entered in the Electronic Data Capture (EDC) system. If required, in the event of a Quality Assurance audit, auditor(s) may be granted access to electronic records.
    - In cases where validated and secure electronic access to the participant's electronic records is not available, unredacted Source Documents (including ICF, Regulatory Documents and Source data) will be uploaded into a regulatory and data privacy-compliant cloud environment, generating certified copies of source documents (as per ICH/GCP guidelines) to be verified by the Clinical Research Associate against the information entered in the Electronic Data Capture (EDC). As per ICH/GCP guidelines, the Principal Investigator and site staff users remain in control of the Source Documents, only site personnel can upload or invalidate source data, while only Clinical Research Associates (or

auditors, as required) assigned to a given site can view the Source Documents remotely.

8.1. Efficacy

Not Applicable.

8.2. Screening Period

Informed consent must be obtained before conducting any study procedures. Screening will be performed within 1 day prior to dosing and include the assessments outlined in the Schedule of Activities (Section 1.3).

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

8.2.1. Medical History

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

COVID-19 disease history, including date of onset and signs and symptoms of COVID-19 as detailed in the eCRF will be collected.

8.2.2. Physical Examinations

A complete physical examination will be performed at Screening and on Day 1. The physical exam only needs to be performed once if Screening and dosing occur on the same day.

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

8.2.3. SARS-CoV-2 Diagnostic Testing

Documentation of laboratory-confirmed SARS-CoV-2 infection via a validated molecular diagnostic test (e.g. RT-PCR) from any respiratory specimen collected ≤7 days prior to study entry must be confirmed for eligibility. This can include tests conducted in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent or from a validated CLIA-waived platform (e.g. Cepheid Gene Xpert Xpress SARS-CoV-2 assay).

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

8.2.4. Secondary Contact Information

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

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

8.3. Virologic Assessments

Part A:

Saliva samples and nasal (mid-turbinate) swabs from participants will be collected for qRT-PCR for virologic assessments at timepoints noted in the Schedule of Activities (Days 1, 2, 5, 8, 11, 15, 22, and 29) (Section 1.3).

For the purpose of resistance surveillance analysis, next generation sequencing analysis of the spike protein of SARS-CoV-2 will be performed on all Day 1 (baseline) mid-turbinate swabs and at the last timepoint with virus above the limit for the sequencing assay for all participants up to Day 8 and an additional timepoint will be sequenced up to Day 29 if still above the limit for the sequencing assay. Other time points may also be subjected to sequence analysis as needed. Susceptibility of suspected resistant variants will be analyzed in a pseudo-virus phenotype assay.

A blood sample for anti-SARS-CoV-2 antibody testing will also be collected on Day 1 pre-dose to allow for exploratory sub-analysis of the virologic endpoints stratified based on antibody response at baseline. A post-baseline blood sample at Day 29 will also be collected to investigate the effect of VIR-7831 on the development of anti-N SARS-CoV-2 antibody.

Part B and Part C:

Nasopharyngeal (NP) swabs from participants will be collected for qRT-PCR for virologic assessments at timepoints noted in the Schedule of Activities (Days 1, 2, 3, 5, 8, 11, 15, 22, and 29) (Section 1.3).

For the purpose of resistance surveillance analysis, next generation sequencing analysis of the spike protein of SARS-CoV-2 will be performed on all Day 1 (baseline) NP swabs and at the last timepoint with virus above the limit for the sequencing assay for all participants. Other time points may also be subjected to sequence analysis as needed.

Susceptibility of suspected resistant variants will be analyzed in a pseudo-virus phenotype assay.

For the secondary endpoint of "Proportion of individuals with a persistently high viral load at Day 8 as assessed via qRT-PCR in nasopharyngeal swab samples", a persistently high viral load will be defined using data from the COMET-ICE study. Viral load data from the COMET-ICE study will be examined and a value and time period for the persistently high viral load will be determined.

A blood sample for anti-SARS-CoV-2 antibody testing will also be collected on Day 1 pre-dose to allow for exploratory sub-analysis of the virologic endpoints stratified based on antibody response at baseline. A post-baseline blood sample at Day 29 will also be collected to investigate the effect of VIR-7831 on the development of anti-N SARS-CoV-2 antibody.

8.4. Safety Assessments

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

Part A:

While the primary safety endpoint is through Day 29, given that this is when the majority of AEs/AESIs (e.g., IRRs) would be expected to occur, safety assessments will continue through Week 36.

Part B and Part C:

Secondary safety endpoints will be through Day 29 and End of Study (Week 36).

8.4.1. Vital Signs

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

Part A:

Vital signs will be monitored within 1 hour prior to and every 15 minutes over the 1 hour IV infusion. Vital signs will also be monitored at approximately 1, 2, 6, and 8 hours after infusion.

Part B:

Vital signs will be monitored within 1 hour prior to administration of study intervention (IM injection or the 15 minute IV infusion). For the Lead-in phase, vital signs will be monitored at end of infusion (IV infusion only) and approximately 30 minutes, 1 hour, and 2 hours after administration of study intervention (infusion or IM injection). For the Expansion phase after the JSRT recommendation that was received on 13 May 2021 to reduce monitoring time, vital signs will be monitored at the end of infusion (IV infusion

only) and approximately 30 minutes and 1 hour after administration of study intervention (infusion or IM injection).

Part C:

Vital signs will be monitored within 1 hour prior to administration of study intervention (IM injection or the 15 minute IV infusion). For the Lead-in phase, vital signs will be monitored at end of infusion (IV infusion only) and at approximately 30 minutes and 1 hour after administration of study intervention (infusion or IM injection). For the Expansion phase, pending JSRT recommendation to reduce monitoring time, vital signs will be monitored at the end of infusion (IV infusion only) and approximately 30 minutes after administration of study intervention (infusion or IM injection).

8.4.2. Electrocardiograms

For Parts A, B, and C of the study, electrocardiograms will be performed locally as outlined in the Schedule of Activities (see Section 1.3). The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding on ECGs should be reported as an AE.

Twelve-lead ECGs will be obtained at each planned ECG assessment during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

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.

At Screening, a single 12-lead ECG is required.

On the day of administration of study intervention, a 12-lead triplicate ECG will be performed before the infusion or injection and within 30 minutes post-injection or the end of infusion:

- Twelve-lead ECGs will be performed with the participant in a semi-supine position after being at rest for at least 10 minutes.
- At each time point at which triplicate ECGs are required, 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 Screening occurs on the same day as the infusion, only the 12-lead triplicate ECGs need to be performed.

At all other time points a single 12-lead ECG will be performed.

Triplicate 12-lead ECGs should be performed as clinically indicated throughout the study, if an ECG abnormality is detected post baseline.

8.4.3. 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 EDC forms.

8.4.4. Hospitalization and Death Data Collection

A hospitalization event and the clinical care that is received during a hospitalization as well as death are components of safety endpoints. Data from the hospitalization and/or death should be captured in the EDC system including but not limited to:

1. Serious Adverse Event (SAE) form
2. Dates that the participant is hospitalized and discharged
3. Dates that the participant is admitted to an intensive care unit
4. Ventilatory support that the participant received
5. Date, time, and cause of death

8.4.5. Active Monitoring of COVID-19 Progression

Following study intervention administration, study participants will be followed up as noted in the Schedule of Activities (Section 1.3) via home nursing (Part B and Part C only) or clinic visits for all visits except Week 16 and Week 36 for Part A; Week 6, Week 16, and Week 36 for the Part B and Part C Lead-in phases; and Week 6, Week 8, Week 16, and Week 36 for the Part B and Part C Expansion phases; which will be conducted via site phone calls. During these assessments, participants will be monitored for progression of disease. This will include questions regarding serious or life-threatening conditions such as dyspnea at rest or severe dyspnea on exertion, hemoptysis, cyanosis, or mental status changes. If a participant exhibits any of these symptoms, the home nurse and/or site will direct the participant to seek medical attention. In addition, any healthcare encounters or new concomitant medications will be recorded.

Participants will also be monitored during these visits/phone calls for subsequent COVID-19 illness (potential re-infection) after Day 29. These assessments will determine whether the participant was diagnosed again with COVID-19 and whether this illness resulted in any healthcare encounters. Any medications given as a result of this illness will also be recorded.

8.4.6. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.
- Laboratory assessments for safety purposes will be performed as noted in the Schedule of Activities (Section 1.3).

- To ensure timely safety management of the participants, laboratory assessments will be performed more frequently during Week 1 as outlined in the Schedule of Activities.
- Urine will be collected on Day 1 (pre-dose) and Day 2 for analysis of albumin to creatinine ratio.
- All protocol-required laboratory tests performed, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and Schedule of Activities (Section 1.3)
  - The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
  - Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
  - All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 days after the 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 clinically significant values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.

8.4.7. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at Screening to confirm eligibility and at Week 24 or 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.

8.4.8. Local Injection Site Tolerability

For IM injections in Part B and Part C 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 pain/tenderness, swelling, redness, bruising, and pruritus. A local injection site tolerability assessment tool is provided in Section 10.5.

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.

Part B:

For the Part B Lead-in phase, the injection sites will be marked and mapped for later observation and should be documented. The tolerability assessment will be performed approximately 1 hour and 2 hours following study drug administration and at Days 2 and 3 per the Schedule of Activities (Section 1.3).

For the Part B Expansion phase after the JSRT recommendation that was received on 13 May 2021 to reduce the monitoring time for Part B, a local injection site tolerability assessment will be performed approximately 1 hour after injection. Any ISRs will need to be followed by the principal investigator (PI) for resolution. If the participant had a severe ISR on Day 1, the participant should be assessed on Day 2 or Day 3 by the investigator.

Part C:

For the Part C Lead-in phase, the injection sites will be marked and mapped for later observation and should be documented. The tolerability assessment will be performed approximately 1 hour following study drug administration and at Days 2 and 3 per the Schedule of Activities (Section 1.3).

For the Part C Expansion phase, a local injection site tolerability assessment will be performed approximately 30 minutes after injection, pending JSRT recommendation to reduce monitoring time. Any ISRs will need to be followed by the PI for resolution. If the participant had a severe ISR on Day 1, the participant should be assessed on Day 2 or Day 3 by the investigator.

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

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

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

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

Hospitalization will be collected and reported as SAEs as delineated in Section 8.5.1 below. Since it will not be possible to delineate in a single participant whether the hospitalization is directly related to COVID-19 complications or could be related to VIR-7831 causing more severe disease due to ADE, all hospitalizations regardless of cause will be counted as SAEs with the exception of hospitalization for:

- elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE as noted in Section 10.3, or
- adverse events related to expected progression, signs, or symptoms of COVID-19 as noted in Section 8.5.8.

All deaths, regardless of cause, will be reported and collected as SAEs.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7). As noted in Section 8.4.4 data on hospitalization or death should additionally be recorded in the eCRF for all relevant sections.

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

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

- All AEs will be collected through Week 12 post-dose. SAEs and AESIs will be collected from dose administration through the Week 36 follow-up visit at the time points specified in the Schedule of Activities (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedure, invasive tests or change in existing therapy) will be recorded from the time the participant consents to participate in the study.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor or designee.

8.5.2. Assessment of Severity

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

8.5.3. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.4. 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 8.5.9), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.5.5. Regulatory Reporting Requirements for SAEs

GlaxoSmithKline (GSK) is acting on behalf of Vir for the purposes of global safety reporting for this study.

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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.5.6. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until Week 36 or the Early Withdrawal visit.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to sponsor or designee within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant will be followed to determine the outcome of the pregnancy. 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 sponsor or designee.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor or designee as described in Section 8.5.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.5.7. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.5.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Adverse events related to expected progression, signs, or symptoms of COVID-19, unless more severe than expected for the participant's current clinical status and medical history, should not be reported as an AE or SAE. These should be collected as disease-related events in the specific eCRF and through Week 36 (EOS).

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

For example, the following constitute events NOT meeting the AE definition and that should be collected as disease-related events:

- hypoxemia due to COVID-19 requiring supplemental oxygen

- hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices

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

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

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

Any death should be recorded and reported as an SAE, and not as a disease-related event.

8.5.9. Adverse Events of Special Interest

Adverse events of special interest are defined in the study protocol as relevant known toxicities of other therapeutic mAbs or as a result of signals observed from previous studies in the nonclinical programs of VIR-7831 that will be monitored by the Sponsor either during or at the end of the study. These will be updated during the course of the study based on accumulating safety data.

AESI include:

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

8.5.9.1. Infusion-Related Reactions and Serious Hypersensitivity

Guidelines for monitoring relevant adverse events 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 hypersensitivity reactions 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.

8.5.9.2. Injection Site Reactions

Part B:

Any ISRs occurring within 2 hours in the Part B Lead-in phase or the Expansion phase prior to JSRT recommendation to reduce the monitoring time, or within 1 hour post-dose

in the Expansion phase after the JSRT recommendation to reduce the monitoring time (received on 13 May 2021), will be considered as solicited AEs and will be reported as clinical events. ISRs occurring after 2 hours post-dose in the Lead-in phase or the Expansion phase prior to JSRT recommendation to reduce the monitoring time, or after 1 hour post-dose in the Expansion phase after the JSRT recommendation to reduce the monitoring time (received on 13 May 2021), will be considered as unsolicited AEs and will be reported as described in Section 10.3.1.

Part C:

Any ISRs occurring within 1 hour in the Part C Lead-in phase or the Expansion phase prior to JSRT recommendation to reduce the monitoring time, or within 30 minutes post-dose in the Expansion phase after the JSRT recommendation to reduce the monitoring time, will be considered as solicited AEs and will be reported as clinical events. ISRs occurring after 1 hour post-dose in the Lead-in phase or the Expansion phase prior to JSRT recommendation to reduce the monitoring time, or after 30 minutes post-dose in the Expansion phase after the JSRT recommendation to reduce the monitoring time, will be considered as unsolicited AEs and will be reported as described in Section 10.3.1.

8.5.9.3. Immunogenicity

Therapeutic proteins, including mAbs, have the potential to induce an unwanted immune response (immunogenicity) in humans. This reaction leads to production of anti-drug-antibodies (ADA) which may inactivate the therapeutic effects of the treatment and, in rare cases, induce adverse events. This study will include participant follow-up for a period of 24 weeks to assess for the development of ADA and potential impacts on safety, PK and/or efficacy.

8.5.9.4. Antibody-Dependent Enhancement

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

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

The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations [Arvin, 2020]. This study will include participant follow-up for a period of 36 Weeks to assess for the potential of enhanced disease in the context of waning VIR-7831 levels, which may manifest as an increased incidence of re-infection or increased severity of re-infections after recovery from initial illness. The third mechanism is hypothesized to occur at high levels of antigen (i.e., viral load) and antibody potentially leading to immune complex deposition and complement activation in tissue sites of high

viral replication. This may manifest as acute deterioration in clinical status temporally associated with VIR-7831 infusion or as increased severity or duration of illness in VIR-7831-treated participants compared to what would be clinically expected.

As described in Section 2.3.1, AEs potentially related to ADE of the disease will be reviewed by the JSRT to assess if there is a greater than expected incidence of re-infection or disease severity.

8.6. Pharmacokinetics

Blood samples for serum PK will be collected from predose Day 1 to Day 169 as detailed in the Schedule of Activities (Section 1.3) and Table 6. Instructions for the collection and handling of biological samples will be provided by the sponsor or designee in the laboratory manual.

- The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of VIR-7831 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 VIR-7831, one sample of sufficient volume can be used.
- VIR-7831 serum concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Table 6 Timeline of Sample Collection for Pharmacokinetic Analysis

		W1				W2			W3	W4	W6	W8	W12	W16	W20	W24
Study Part	**Screening (Day 0/1)**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 11**	**Day 15 ± 1d**	**Day 22 ± 1d**	**Day 29 ± 2d**	**Day 43 ± 3d**	**Day 57 ± 4d**	**Day 85 ± 7d**	**Day 113 ± 7d**	**Day 141 ± 7d**	**Day 169 ± 7d**
Part A		X[a]	X		X	X		X		X	X	X	X		X	X
Part B Lead-in phase		X[b]	X	X	X	X		X		X		X	X		X	X
Part B Expansion phase		X[b]		X		X		X		X			X		X	X
Part C Lead-in phase		X[b]	X	X	X	X		X		X		X	X		X	X
Part C Expansion phase		X[b]		X		X		X		X			X		X	X

a. On Day 1, sample collection will occur pre-dose, end of infusion, and at approximately 1, 2, 6, and 8 hours following end of infusion. On other days, samples will be collected once daily.
b. On Day 1, sample collection will occur pre-dose (IM and IV) and at end of infusion (IV only). On other days, samples will be collected once daily.

For intensive PK in Part A and the Lead-in phases of Parts B and C, PK parameters will be computed using standard noncompartmental methods. Parameters may include, but are not limited to C_{max}, C_{last}, T_{max}, T_{last}, $AUC_{D1\text{-}29}$, AUC_{inf}, AUC_{last}, $\%AUC_{exp}$, $t_{1/2}$, λ_z, V_z (IV), apparent volume of distribution at steady state (V_{ss}; IV), apparent volume (V/F; IM), apparent clearance (CL/F; IM), bioavailability (F) and will be listed and summarized

using descriptive statistics. Other parameters may be calculated, if deemed necessary. Definitions of PK parameters, methods for estimation and details of PK analyses for each study Part will be included in the analysis plan.

Serum concentrations may be combined with data from other studies evaluating VIR-7831 for the purpose of population PK model development. These analyses may include graphical plots, tabular summaries, and various linear and/or nonlinear analyses. Details of the PK analyses will be provided in the Population PK analysis plan.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. Health Economics

Not applicable.

8.10. Immunogenicity Assessments

Antibodies to VIR-7831 will be evaluated in serum samples collected from all participants according to the Schedule of Activities (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or designee.

Serum samples will be screened for antibodies binding to VIR-7831 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to VIR-7831 and/or further characterize the immunogenicity of VIR-7831.

The detection and characterization of antibodies to VIR-7831 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 VIR-7831 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor/designee to enable analysis of immune responses to VIR-7831 as described.

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

8.11. Resistance Analyses

In order to monitor for potential resistance to VIR-7831, resistance surveillance will be conducted for all participants at baseline and certain follow-up specimens (nasal mid-turbinate in Part A, and NP in Parts B and C). Deep sequence analysis of the SARS-CoV-2 spike gene may be attempted on nasopharyngeal or nasal mid-turbinate samples to determine amino acid variants. For identified substitutions that qualify for phenotypic analysis, the antiviral activity of VIR-7831 will be evaluated in vitro using a SARS-CoV-2 spike pseudovirus system.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Part A Statistical Hypotheses

The primary objective of Part A of the study is to evaluate the safety and tolerability of VIR-7831 Gen2 material. Secondary objectives are to evaluate the pharmacokinetics and virologic profile of VIR-7831. There are no formal hypothesis tests associated with these objectives and no formal significance tests or comparisons will be made between the two treatment groups.

9.1.2. Part B Statistical Hypotheses

The primary objective of Part B of the study is to evaluate the viral pharmacodynamics of VIR-7831 Gen2 material administered via IV infusion and IM injection, specifically via assessments of $\log_{10}$ SARS-CoV2 viral load $AUC_{(D1\text{-}8)}$ following a single dose of 500 mg IV or a single dose of 500 mg IM. The time period of 8 days has been selected to optimize the sensitivity of the AUC signal given the propensity for negative PCR results in the majority of trial participants by Day 28 [Chen, 2021]. Secondary objectives include evaluating the safety, tolerability, and pharmacokinetics of VIR-7831 Gen2 material administered via IM injection.

9.1.3. Part C Statistical Hypotheses

The primary objective of Part C of the study is to evaluate the viral pharmacodynamics of VIR-7831 Gen2 500 mg IV compared to Gen2 250 mg IM, specifically via assessments of $\log_{10}$ SARS-CoV2 viral load $AUC_{(D1\text{-}8)}$ following a single dose of 500 mg IV or a single dose of 250 mg IM. Similar to Part B, the time period of 8 days has been selected to optimize the sensitivity of the AUC signal given the propensity for negative PCR results in the majority of trial participants by Day 28 [Chen, 2021]. Secondary objectives include evaluating the safety, tolerability, and pharmacokinetics of VIR-7831 Gen2 material administered via IM injection.

9.2. Sample Size Determination

9.2.1. Part A Sample Size Determination

Approximately 40 participants will be randomized in a 3:1 ratio to VIR-7831 Gen2 or Gen1 material.

The sample size is based on practical considerations, i.e., experience with similar types of studies that allow for reasonable qualitative data. No formal sample size calculations were performed; however, a sample size of 40 subjects (30 Gen2, 10 Gen1) should provide suitable assessment of the descriptive safety, tolerability and PK profile for VIR-7831 Gen2. Table 7 shows examples of the precision in the estimated AE rate on the Gen2 arm.

Table 7 Precision in the Estimated AE Rate (Gen2) for Part A

Number of Gen2 participants with ≥1 AE (N=30)	AE Rate	Exact 95% CI
3	10%	2.1%, 26.5%
6	20%	7.7%, 38.6%
15	50%	31.3%, 68.7%

9.2.2. Part B Sample Size Determination

Approximately 150 participants will be randomized in a 1:1 ratio to VIR-7831 Gen2 IV or IM. The sample size is based on enabling a comparison of $\log_{10}$ SARS-CoV2 viral load $AUC_{(D1\text{-}8)}$ following a single dose of 500 mg IV or a single dose of 500 mg IM that will be made based on the treatment ratio 90% confidence interval falling within pharmacological equivalence bounds of 0.5 to 2.0 and assumed coefficient of variation of 200% and the true ratio is 1. The margin of 0.5 to 2.0 is deemed appropriate for the comparison of viral load due to the endpoint being a variable PD endpoint. Table 8 presents the sensitivity of power for different values of coefficient of variations, given the same sample size of 75 participants per arm.

Table 8 Sample Size Sensitivity Assessment for Part B

Equivalence Bound Range	Sample Size Per Arm	Coefficient of Variation (%)	Power (%)
0.5-2.0	75	150	98
		180	94
		200	91
		220	88
		250	83

9.2.3. Part C Sample Size Determination

Approximately 150 participants will be randomized in a 1:1 ratio to VIR-7831 Gen2 500 mg IV or 250 mg IM. The sample size is based on enabling a comparison of $\log_{10}$

SARS-CoV2 viral load $AUC_{(D1-8)}$ following a single dose of 500 mg IV or a single dose of 250 mg IM that will be made based on the treatment ratio 90% confidence interval falling within pharmacological equivalence bounds of 0.5 to 2.0 and assumed coefficient of variation of 200% and the true ratio is 1. The margin of 0.5 to 2.0 is deemed appropriate for the comparison of viral load due to the endpoint being a variable PD endpoint. Table 9 presents the sensitivity of power for different values of coefficient of variations, given the same sample size of 75 participants per arm.

Table 9 Sample Size Sensitivity Assessment for Part C

Equivalence Bound Range	Sample Size Per Arm	Coefficient of Variation (%)	Power (%)
0.5-2.0	75	150	98
		180	94
		200	91
		220	88
		250	83

9.3. Analysis Sets

9.3.1. Part A Analysis Sets

Participant Analysis Set	Description
Randomized	All participants who were randomly assigned to study intervention in the study. Data should be reported according to the randomized intervention.
Safety	All randomized participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analyzed according to the intervention they actually received.
Virology	All participants in the Safety analysis set with a central lab confirmed quantifiable nasal mid-turbinate and/or saliva swab at baseline. Data should be reported according to the intervention they actually received.

9.3.2. Part B and Part C Analysis Sets

Participant Analysis Set	Description
Randomized	All participants who were randomly assigned to study intervention in the study. Data should be reported according to the randomized intervention.

Participant Analysis Set	Description
Safety	All randomized participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
Viral Pharmacodynamic (PD)	All participants in the Safety analysis set who had a baseline (Day 1) quantifiable viral load as assessed using qRT-PCR from NP swabs. Data should be reported according to the intervention they actually received.
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

9.4.1. General Considerations

9.4.1.1. Part A, Part B, and Part C General Considerations

The statistical analysis plans for Part A, Part B and Part C will include a more detailed description of the statistical analyses described in this section. Results from these three Parts will be reported separately. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.2. Primary Endpoint(s)

9.4.2.1. Part A Primary Endpoint(s)

Adverse events (AEs) will be coded using the standard GSK dictionary, Medical Dictionary for Regulatory Activities (MedDRA), and grouped by body system. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug-related AEs, fatal AEs, non-fatal SAEs, adverse events of special interest (AESIs) and AEs leading to withdrawal from study, through to Day 29. Deaths and SAEs, if applicable, will be documented in case narrative format. Occurrence of clinically significant ECG abnormalities through Day 29 will also be summarized.

As part of regular safety assessments during conduct of the study, events deemed by the investigator to be related to expected COVID-19 disease progression and therefore not classified as an AE or SAE (see Section 8.5.8) will also be summarized. Further detail will be provided in the analysis plan.

Possible intercurrent events include withdrawal of consent, lost-to-follow-up and use of non-study therapy for COVID-19. The strategy for analysis for these intercurrent events, will be to use the treatment policy strategy, with data analyzed as collected. The complete

descriptions for intercurrent events and estimand strategies with further details will be provided in the analysis plan.

The primary estimand strategy for primary safety endpoint is provided in Table 10.

Table 10 Primary Estimand Strategy for Primary Safety Endpoint

Primary Estimand	
Objective	Evaluate safety and tolerability of VIR-7831 Gen2 material
Variable/Endpoints	≥1 event (AE, SAE, AESI, ECG abnormality) through Day 29
Participant Analysis Set	Safety
Intercurrent Event Strategy	Data analyzed as collected (treatment policy strategy)
Population Level Summary Measure	Descriptive summary: proportion of participants with ≥1 event through Day 29

9.4.2.2. Part B and Part C Primary Endpoint(s)

The primary endpoints of Part B and Part C will be analyzed separately using different ANCOVA models as stated in this section. The mean of log-transformed AUC of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 8 (AUC_{D1-8}) in NP swab samples will be assessed using an ANCOVA Model with treatments, prior exposure to an authorized or approved SARS-CoV-2 vaccine (for Part C only), and baseline viral load as covariates. The estimated geometric mean ratios and 90% CI of 500 mg IV:500 mg IM in Part B and 500 mg IV:250 mg IM in Part C after back-transformation will also be presented. Further details will be provided in the analysis plan.

The primary estimand strategy for primary PD endpoint is provided in Table 11.

Table 11 Primary Estimand Strategy for Primary PD Endpoint

Primary Estimand	
Objective	Evaluate the virological response of VIR-7831 Gen2 in the upper respiratory tract administered by different routes and doses as planned by Parts B and C separately, without combining the data.
Variable/Endpoints	Log-transformed AUC_{D1-8} of SARS-CoV-2 viral load as measured by qRT-PCR in nasopharyngeal swab samples.
Participant Analysis Set	Pharmacodynamic
Intercurrent Event Strategy	Intercurrent events: Death and Use of other COVID-19 therapies. Strategy for Death: Composite strategy, where subjects who die prior to Day 8, their AUC_{D1-8} viral load value will be

Primary Estimand	
	imputed using the worst AUC viral load value from other subjects in the same treatment arm. The strategy for all the other intercurrent events (as applicable for this endpoint) will be treatment policy where data will be reported as captured.
Population Level Summary Measure	Geometric mean ratios and 90% CI

9.4.3. Secondary Endpoints

9.4.3.1. Part A Secondary Endpoints

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

AEs and clinically significant ECG abnormalities (through Week 12), SAEs, and AESIs through EOS (Week 36) will be summarized in a similar manner as noted for the primary endpoint above.

As part of regular safety assessments during conduct of the study, events deemed by the investigator to be related to expected COVID-19 disease progression (i.e., disease-related events) and therefore not classified as an AE or SAE (see Section 8.5.8) through Week 36 will also be summarized. Further detail will be provided in the analysis plan.

The virology endpoint specific to Part A is the change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from saliva and nasal mid-turbinate swab samples. Summaries of mean viral load and change from baseline will be presented on the $\log_{10}$ scale for Gen1 and Gen2-treated patients at each visit. Further details of the analysis methods for the virology endpoints will be provided in the analysis plan.

9.4.3.2. Part B and Part C Secondary Endpoints

Full details of all analysis methods for the PK endpoints will be provided in the analysis plan. The secondary endpoints in Parts B and C will also be reported separately, without combining the data.

AEs, SAEs, and AESIs through Day 29 and EOS (Week 36 for all except Week 12 for non-serious AEs and clinically significant ECG abnormalities) will be summarized in a similar manner as noted for the primary endpoint analysis of Part A above.

As part of regular safety assessments during conduct of the study, events deemed by the investigator to be related to expected COVID-19 disease progression (i.e., disease-related events) and therefore not classified as an AE or SAE (see Section 8.5.8) through Day 29 and Week 36 will also be summarized. Further detail will be provided in the analysis plan.

The virology endpoints for Part B and C are the change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from NP swab samples, the proportion

of participants with undetectable viral load at all visits through Day 29 as measured by qRT-PCR from NP swab samples, the proportion of participants with a persistently high viral load at Day 8 as measured by qRT-PCR from NP swab samples, and the mean area under the curve of SARS-CoV-2 viral load as measured by qRT-PCR from NP swab samples from Day 1 to Day 5 (AUC_{D1-5}) and Day 1 to 11 (AUC_{D1-11}). In each Part of the study, separate summaries of mean viral load and change from baseline will be presented on the log_{10} scale by treatments at each visit. Further details of the analysis methods for the virology endpoints will be provided in the analysis plan.

9.4.4. Exploratory Endpoints

For Parts A, B and C, incidence and titers (if applicable) of serum anti-drug antibodies (ADA) to VIR-7831 will be assessed. Incidence and titers (if applicable) of serum anti-N SARS-CoV-2 antibodies at Day 29 will also be assessed. Incidence and titers (if applicable) of anti-N, anti-S and anti-RBD SARS-CoV-2 antibodies at baseline will also be assessed. Further details of the analysis methods for the exploratory endpoints will be provided in the analysis plan.

Emergence of SARS-CoV-2 viral resistance mutants will also be assessed. Further details of the analysis methods for the resistance endpoint will be provided in the analysis plan.

9.5. Interim Analysis

No interim analyses will be conducted in this study.

However, in all Parts, once the last participant recruited completes the primary assessment, the data will be analyzed for a readout of the primary and selected secondary endpoints. Data from different Parts of the study will not be combined for analysis and separate study reports will be prepared, as appropriate. Participants will continue to complete the remaining scheduled assessments.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Clinical Trials Directive 2001/20/EC or Regulation (EU) No. 536/2014 (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

GSK (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 VIR-7831 or about the study disease; fulfill legal and regulatory obligations, including reporting safety information about VIR-7831, this study, and the results of this study to regulatory authorities; provide information about the safety and use of VIR-7831 to investigators and institutions that plan to administer VIR-7831 to patients; publish the results of these research efforts; work with government agencies or insurers to have VIR-7831 approved for medical use or approved for payment coverage.

10.1.4. Data Protection

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

10.1.5. Committees Structure

10.1.5.1. Joint Safety Review Team (JSRT)

The JSRT, comprised of team members from clinical research, pharmacovigilance, and statistics from Vir and GSK, will review blinded safety data from Part A of the study at regular intervals. For Parts B and C of the study, the JSRT will be unblinded, and data will be reviewed according to the Treatment-Sensitive Data Plan for Open-Label Randomized Study. There will be no routine in-stream review of aggregated safety data by treatment arm at any JSRT meeting other than at the two Post-Day 3 JSRT meetings (one for Part B and one for Part C) that will determine if the monitoring time may be reduced. Additionally, any sharing of potential safety signals will reflect pooled data that is not separated by treatment arm. The Safety team may need to review single unblinded case reports to support regulatory reporting obligations. Details regarding the JSRT process will be available in relevant SRT documents.

10.1.6. Dissemination of Clinical Study Data

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory

data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the printed CRFs or entered in the electronic eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in 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

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

Refer to 10.7.1 for additional Germany-specific information regarding study and site termination.

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 Section 1.3 will be performed by either the central laboratory or the site local laboratory.

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

Table 12 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**			
	Hematocrit	ABO typing[1]	Urine albumin to creatinine ratio[2]	
Hematology	Platelet Count RBC Count Hemoglobin	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine[3]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Gamma-glutamyl transferase (GGT)
	Carbon dioxide/bicarbonate	Chloride	Lactate dehydrogenase (LDH)	Albumin
	Amylase	Lipase		
Coagulation parameters	International Normalized Ratio (INR) time	Prothrombin time (PT)	Partial thromboplastin time (PTT) / Activated PTT (aPTT)	
Pregnancy testing	Highly sensitive (Serum/plasma or urine) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			

[1] ABO grouping: If done during the current or previous medical encounter, that data can be used, no additional blood draw should be performed
[2] Repeat if >500 mg/g
[3] Repeat if above normal range

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 hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned when indicated by the protocol, such as those collected in the Local Injection Site Tolerability Assessment and monitoring of COVID-19 disease progression.

Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Clinically significant changes in laboratory assessments.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
    - For example, hypoxemia due to COVID-19 requiring supplemental oxygen, hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices and respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO
- 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 AEs. 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 the following are not considered an AE:

    - elective treatment of a pre-existing condition that did not worsen from baseline, or

    - adverse events related to expected progression, signs, or symptoms of COVID-19 (as noted in Section 8.5.8).

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other medically significant situations:

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

    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to 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.

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, 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 13 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- 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 SAE coordinator 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 SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

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 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 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 ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods 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
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• 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 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 o oral

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
○ intravaginal ○ transdermal ○ injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation ○ 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.*

10.5. Appendix 5: Local Injection Site Tolerability Assessment

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.

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.

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 subject has evidence of necrosis/ulceration, the subject 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 (0.5ml) 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.

References

1. Medical Management of Vaccine Reactions in Adults in a Community Setting, Immunization Action Coalition, https://www.immunize.org/catg.d/p3082.pdf
2. Preventing and Managing Adverse Reactions, General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)
3. Sampson HA Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al, Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391-7

10.7. Appendix 7: Country-specific Requirements

10.7.1. Germany

7.2 Participant Discontinuation/Withdrawal from the Study

The following additional participant discontinuation criterion applies:

i. Participants are to be excluded from further participation if the COVID-19 disease requires hospitalization or treatment with non-permitted medication (please refer to Section 6.8.1 of the protocol), according to §40 paragraph 1 sentence 3 no. 2 German Medicinal Products Act (AMG).

Safety Criteria for Withdrawal of Individual from Study

The criteria leading to termination of a subject or withdrawal of study intervention are provided in Section 7 of the protocol, and include the following:

- **AEs:** For IV administration, a participant will be permanently discontinued from completion of drug infusion if they experience life-threatening, infusion-related reactions including severe allergic or hypersensitivity reactions 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.
- **Grade 2 IRRs:** 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).
- **Withdrawal of consent:** A participant may withdraw from the study at any time at his/her own request, at the request of their LAR, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- **Lost to follow-up:** A participant will be considered lost to follow-up if he or she repeatedly fails to adhere to scheduled visits and is unable to be contacted by the study site. Further details are provided in Section 7.3 of the protocol.

10.1.9 Study and Site Start and Closure

The following additional study termination reason applies:

ii. The study shall also be terminated if the favorable opinion or approval is revoked, according to §42a paragraph 4 in conjunction with paragraph 1, 2 and 4a, German Medicinal Products Act (AMG).

Safety Criteria for Termination of Study

Further information on the reasons for study and/or site termination are provided in Section 10.1.9 of the protocol and includes the following:

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

In addition to the above, a JSRT will review safety data from Part A, Part B and Part C of the study on a regular basis and if the JSRT identifies any serious safety concerns for any Part of the study, including those that may require study termination, these will be escalated to an internal Safety Review Committee, and any actions will be distributed to sites and investigators promptly.

10.7.2. Summary of Changes History for the Germany Country-specific Protocol Amendment

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 03/DEU-01	23-APR-2021	TMF-12551962
Amendment 03	08-APR-2021	TMF-11941318
Amendment 02	03-MAR-2021	TMF-11814330
Amendment 01	19-JAN-2021	TMF-11735674
Original Protocol	10-DEC-2020	2020N457654_00

Amendment 03/DEU-1: 23-APR-2021

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

Overall Rationale for the Amendment: To add country-specific information that was requested by the Germany Ethics Committee.

Section # and Name	Description of Change	Brief Rationale
10.7. Appendix 7: Country-specific Requirements	Added Germany-specific exclusion criteria; clarified participant discontinuation criteria and reasons for study termination	Added information requested by the Germany Ethics Committee

10.8. Appendix 8: Abbreviations and Trademarks

Term	Definition
ADA	Anti-drug antibodies
ADE	Antibody dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
AMG	Medicinal Products Act
Anti-N	Anti-nucleocapsid
Anti-RBD	Anti-receptor binding domain
Anti-S	Anti-spike
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
AUC_{DX-Y}	Area under the curve from Day X to Day Y
AUC_{inf}	Area under the serum concentration-time curve extrapolated from zero to infinity
AUC_{last}	Area under the curve from the time of dosing to the time of the last measurable (positive) concentration
$\%AUC_{exp}$	The extrapolated portion of AUC_{inf}
BP	Blood pressure
BMI	body mass index
C_{last}	Concentration at last quantifiable timepoint.
C_{max}	Maximum observed concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CL/F	Apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
DAIDS	Division of acquired immune-deficiency syndrome

Term	Definition
DP	Drug Product
DS	Drug Substance
DSMB	Data and Safety Monitoring Board
EC_{90}	90% effective concentration
ECG	Electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EU	European Union
EW	Early withdrawal
F	Bioavailability
FcγR	Fc Gamma Receptor
FIH	First-in-human
FPFV	First patient first visit
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
HSR	Hypersensitivity reactions
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional review board
IRR	Infusion related reaction

Term	Definition
IRT	Interactive response technology
ISR	Injection site reaction
ITT	Intent-to-Treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive Web Response System
L	Liter
JSRT	Joint safety review team
LAR	Legally authorized representative
μg	microgram
mg	milligram
mAb	Monoclonal antibody
MARM	Monoclonal antibody-resistant mutant
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MSDS	Material safety data sheet
NP	Nasopharyngeal
NQ	Non-quantifiable
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PI	Principal investigator
PK	Pharmacokinetic(s)
PR	Pulse rate
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
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	Severe acute respiratory syndrome

Term	Definition
SoA	Schedule of activities
SoC	Standard of care
SRM	Study reference manual
SRT	Safety review team
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}
ULN	Upper limit of normal
US	United States
V	Apparent volume of distribution
V/F	Apparent volume
Vir	Vir Biotechnology, Inc.
V_{ss}	Apparent volume of distribution at steady state
V_z	Apparent volume of distribution during the elimination phase
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
Cepheid Gene Xpert Xpress
MedDRA

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 04: 18 May 2021

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

Overall Rationale for the Amendment: Protocol changes have been made to add a third part (Part C) to this study to assess the safety, tolerability, immunogenicity, pharmacokinetics, and viral pharmacodynamics of a 250 mg dose of VIR-7831 administered by intramuscular (IM) injection. Changes were made throughout the protocol to add information necessary for conducting Part C procedures. Additionally, the post-dose monitoring time for Part B has been reduced to 1 hour after Joint Safety Review Team (JSRT) review on 13 May 2021. Other changes include: moving resistance analysis to an exploratory objective, providing updated data, clarification of inclusion and exclusion criteria, incorporated information from the Germany-specific protocol amendment, and other clarifications throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis, 1.2. Schema, 1.3. Schedule of Activities (SoA), 2.1. Study Rationale, 2.2. Background, 2.3.1. Risk Assessment, 2.3.3. Overall Benefit: Risk Conclusion, 3. Objectives and Endpoints, 4.1. Overall Design, 4.2. Scientific Rationale for Study Design, 4.3. Justification for Dose, 4.4. End of Study Definition, 5.1. Inclusion Criteria, 5.2. Exclusion Criteria, 6.1. Study Intervention(s) Administered, 6.3. Measures to Minimize Bias: Randomization and Blinding, 6.8.2. Permitted Concomitant Medication, 8. Study Assessments and Procedures, 8.3. Virologic Assessments, 8.4. Safety Assessments, 8.4.1. Vital Signs, 8.4.2 Electrocardiograms, 8.4.5. Active Monitoring of COVID-19 Progression, 8.4.8. Local Injection Site Tolerability, 8.5.9.2. Injection Site Reactions, 8.6. Pharmacokinetics, 8.11. Resistance Analyses, 9.1.3. Part C Statistical Hypotheses, 9.2.3. Part C Sample Size Determination, 9.3.2. Part B and Part C Analysis Sets, 9.4.1.1. Part A, Part B, and Part C General Considerations, 9.4.2.2. Part B and Part C Primary Endpoint(s), 9.4.3.2. Part B and Part C Secondary Endpoints, 9.4.4. Exploratory Endpoints, 9.5. Interim Analysis, 10.1.5.1. Joint Safety Review Team (JSRT), 10.7.1. Germany	Added information regarding the Part C endpoints, objectives, rationale, background, inclusion and exclusion criteria, number of participants, intervention groups and duration, JSRT, study design, study procedures, dose rationale, risk assessment, and statistical analyses to applicable sections. Updated the study schema and added a Schedule of Activities table for Part C.	Added study Part C to gain clinical experience with 250 mg VIR-7831 administered via IM injection
1.1. Synopsis, 1.3. Schedule of Activities (SoA), 4.1. Overall Design, 8.4.1. Vital Signs, 8.4.8. Local Injection Site Tolerability, 8.5.9.2. Injection Site Reactions	Updated with JSRT recommendation to reduce Part B post-dose monitoring to 1 hour.	Updated based on the 13 May 2021 JSRT recommendation to reduce the post-dose monitoring time for Part B to 1 hour.

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Updated Exclusion Criteria number 10 to clarify when SARS-CoV-2 vaccine is permitted for each Part of the study.	To clarify exclusion criteria
5.1. Inclusion Criteria, 5.2. Exclusion Criteria	Added South Korea- and Germany-specific inclusion and exclusion criteria.	Added country-specific inclusion and exclusion criteria into the main body of the global protocol
7.2. Participant Discontinuation/Withdrawal from the Study, 10.1.9. Study and Site Start and Closure, 10.7. Appendix 7: Country-specific Requirements; 10.7.1. Germany, 10.7.2. Summary of Changes History for the Germany Country-specific Protocol Amendment	Incorporated Germany-Specific language into the global protocol.	To provide information from the Germany country-specific amendment in the global protocol
6.8.1. Medication Not Permitted During the Study, 6.8.2. Permitted Concomitant Medication	Further described the permitted and prohibited receipt of SARS-CoV-2 vaccines during each Part of the study.	To clarify the permitted and prohibited receipt of SARS-CoV-2 vaccines
1.1. Synopsis, 1.2. Schema, 3. Objectives and Endpoints, 9.4.3.1. Part A Secondary Endpoints, 9.4.3.2. Part B and Part C Secondary Endpoints, 9.4.4. Exploratory Endpoints	Resistance analysis was moved from a secondary to an exploratory objective and removed from the schematic.	Given the small number of expected events for this endpoint, resistance analysis was moved from a secondary objective to an exploratory objective
1.1. Synopsis, 3. Objectives and Endpoints	Added ‘presence at baseline’ to the endpoint for the resistance objective.	Added detail to the resistance endpoint to match the objective
10.3.4. Recording and Follow-Up of AE and SAE	Changed assessment of severity to Division of Acquired Immune-Deficiency Syndrome (DAIDS) grading.	Corrected information

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis, 1.2. Schema, 4.1. Overall Design, 4.2. Scientific Rationale for Study Design, 10.1.5.1. Joint Safety Review Team (JSRT)	Clarified the JSRT data review for Parts B and C.	To clarify JSRT review of data
7.1. Discontinuation of Study Intervention	Specified that participants should be permanently discontinued from study drug intervention if they experience a Grade 3 or 4 infusion-related reaction.	To clarify study intervention discontinuation
8.3. Virologic Assessments	Added details regarding the timepoints for sequencing analysis for Part A.	To clarify virologic assessments
1.1. Synopsis, 8.4.1. Vital Signs	Updated wording of Part B study procedures.	To clarify study procedures and for consistency throughout the document
8.5. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting	Used bullet points for the exceptions to reporting hospitalization as an SAE.	To clarify when hospitalization is not considered an SAE
10.3.2. Definition of an SAE	Added the exceptions to reporting hospitalization as an SAE.	To align with Section 8.5.
8.5. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting, 8.5.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Added text to clarify that all deaths are considered SAEs.	To clarify that all deaths should be considered SAEs
10.3.1. Definition of AE	Updated the descriptions of solicited and unsolicited adverse events.	Updated the descriptions for solicited and unsolicited adverse events because participant diaries are not used in this study

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis, 2.1. Study Rationale; 2.2. Background, 2.3.2. Benefit Assessment, 2.3.3. Overall Benefit: Risk Conclusion, 4.3. Justification for Dose	Provided updated information from BLAZE-4 and COMET-ICE. Provided updated numbers for COVID-19 cases and deaths. Removed bamlanivimab from the list of monoclonal antibodies that have emergency use authorization for COVID-19. Provided updated information about other planned studies for IM VIR-7831.	To provide the most current information
Title Page, Sponsor Signatory Page, 1.1. Synopsis, 2.1. Study Rationale, 6.1. Study Intervention(s) Administered	Added sotrovimab to the list of names for the investigational product.	Added the international nonproprietary name
6.1. Study Intervention(s) Administered	Corrected GSK compound number.	Corrected typographical error
9.4.2.2. Part B and Part C Primary Endpoint(s)	Updated intercurrent events.	To align with the statistical analysis plan
9.4.2.2. Part B and Part C Primary Endpoint(s)	Changed model from ANOVA to ANCOVA.	Corrected typographical error
9.4.3.1. Part A Secondary Endpoints, 9.4.3.2. Part B and Part C Secondary Endpoints	“Disease-progression events’ was changed to “disease-related events”	Corrected wording
9.4.1.1. Part A, Part B, and Part C General Considerations, 9.5. Interim Analysis	Provided details regarding the planned data readouts for Parts A, B, and C and specified that results from each Part will be reported separately.	Clarified the data readout plan and reporting
8.6. Pharmacokinetics	Specified which parameters are to be assessed for intravenous infusions and intramuscular injections.	To clarify pharmacokinetic assessments

Section # and Name	Description of Change	Brief Rationale
10.7. Appendix 7: Country-specific Requirements	Added level 3 numbered headings.	Headings added to improve readability
10.7. Appendix 7: Country-specific Requirements	Removed country-specific inclusion and exclusion criteria from this section.	Country-specific inclusion and exclusion criteria were moved to Section 5.1. and Section 5.2., respectively
10.7. Appendix 7: Country-specific Requirements	Removed South Korea from Appendix 7.	All South Korea-specific information has been incorporated into Section 5.1. and Section 5.2
8.4.2. Electrocardiograms	Changed a statement from “on the day of infusion” to “on the day of administration of study intervention”.	Updated for clarity because this statement applies to both IV and IM administration of study intervention
10.8. Appendix 8: Abbreviations and Trademarks	Added additional abbreviations.	Updated abbreviation list to match abbreviations used in-text
11. References	Added and removed references.	Updated the reference list to match in-text citations
All sections	Other minor grammatical and typographical corrections.	To improve readability

Amendment 03: 08-APR-2021

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

Overall Rationale for the Amendment: Adding measurement of anti-SARS-CoV-2 antibody at baseline and Day 29 to the study procedures to allow for exploratory analysis of immune response. Removing the requirement that at least 15 participants are enrolled in Part A before enrollment in Part B can begin so that Part B can begin without delay.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis, 1.3. Schedule of Activities, 3. Objectives and Endpoints, 8.3 Virologic Assessments, 9.4.4. Exploratory Endpoints	Added measurement and analyses of anti-SARS-CoV-2 antibody at baseline and Day 29 to study Parts A and B. Added an exploratory objective and endpoints to assess the effect of VIR-7831 on immune response.	To allow for exploratory sub-analysis of virologic endpoints based on antibody response at baseline. To evaluate the effect of VIR-7831 on development of antibody (immune response) at Day 29.
1.1. Synopsis, 3. Objectives and Endpoints	Clarified that the secondary objective to monitor for emergence of resistance mutants to VIR-7831 will also monitor presence at baseline.	To clarify the intention of the secondary objective to monitor resistance.
1.1. Synopsis, 1.2 Schema, 2.1. Study Rationale, 4.1. Overall Design	Removed the requirement that at least 15 participants are enrolled in Part A before enrollment in Part B can begin.	To permit selected sites to begin enrolling to Part B without delay.
5.1 Inclusion Criteria	Updated wording of inclusion criteria 1 to state that the age restriction for Part B is for logistical purposes related to study COMET-TAIL instead of COMET ICE.	COMET-ICE is no longer enrolling patients, but COMET-TAIL will enroll a similar population as COMET PEAK.
1.1. Synopsis, 2.1. Study Rationale, 2.3.1. Risk Assessment, 2.3.2. Benefit Assessment, 2.3.3. Overall Benefit: Risk Conclusion, 4.3. Justification for Dose, 6.1. Study Intervention(s) Administered	Provided updated information from the COMET-ICE, BLAZE-4, and ACTIV-3 studies	Provided updated information.
1.1. Synopsis, 2.1. Study Rationale, 2.3.2 Benefit Assessment, 6.1. Study Intervention(s) Administered	Changed language regarding enrollment, randomization, and VIR-7831 administration in the COMET-ICE and ACTIV-3-TICO studies to past tense.	COMET-ICE and ACTIV-3-TICO are no longer enrolling participants. No new administration of VIR-7831 will occur in COMET-ICE or ACTIV-3-TICO.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Specified that Part B will enroll participants 18 to <70 years of age.	Corrected wording to match the inclusion criteria.
8.6. Pharmacokinetics	Added 'approximately;' to footnote a for Table 5.	Corrected footnote to match the corresponding footnote in the Schedule of Activities table.
Title page, 1.1. Synopsis	Defined abbreviations IV, IM, and COVID-19 in the brief title.	To clarify the brief title.
All sections	Other minor grammatical and typographical corrections.	To improve readability.

Amendment 02: 03-MAR-2021

Overall Rationale for the Amendment: Protocol changes have been made to add a second part (Part B) to this study to assess intramuscular (IM) injection of VIR-7831 Gen2 material. The original treatment arms evaluating Gen2 and Gen1 material administered IV is designated Part A. Changes were made throughout the protocol to add information necessary for conducting Part B and to differentiate Part A and Part B procedures. Other changes include: removal of home nursing option for Part A study visits, an additional endpoint for the secondary safety objective for Part A, updates to endpoint wording for Part A, the addition of resistance analyses, updated background information based on new data, and clarifications throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis, 1.2. Schema, 1.3. Schedule of Activities, 2.1. Study Rationale, 2.2. Background, 2.3.1. Risk Assessment, 2.3.2. Benefit Assessment, 2.3.3. Overall Benefit: risk Assessment, 3. Objectives and Endpoints, 4.1. Overall Design, 4.2. Scientific Rationale for Study Design; 4.3. Justification for Dose, 4.4. End of Study Definition, 5.1 Inclusion Criteria, 5.2. Exclusion Criteria, 6.1. Study Intervention(s) Administered, 6.3. Measures to Minimize Bias: Randomization and Blinding, 6.4. Study Intervention Compliance, 8. Study Assessments and Procedures, 8.3. Virologic Assessments, 8.4. Safety Assessments; 8.4.1. Vital Signs; 8.4.2. Electrocardiograms, 8.4.5. Active Monitoring of COVID-19 Progression 8.4.8. Local Injection Site Tolerability, 8.6. Pharmacokinetics, 9.1. Statistical Hypotheses, 9.2. Sample Size Determination, 9.3. Analysis Sets, 9.4.1. General Considerations, 9.4.2. Primary Endpoints, 9.4.3 Secondary endpoints, 9.4.4 Exploratory Endpoints, 9.5 Interim Analysis, 10.1.5.1. Joint Safety Review Team (JSRT)	Separated study into Parts A and B. Added information regarding the Part B endpoints, objectives, rationale, number of participants, intervention groups and duration, Joint Safety Review Team, study design, study procedures, background, risk assessment, exclusion criteria, study interventions, and statistical analyses to applicable sections. Updated the study schema and added schedule of Activities tables for the Lead-in and Expansion phases of Part B. Added language to differentiate Part A from Part B.	Added study Part B to gain clinical experience with Gen2 administered via intramuscular (IM) injection.
5.2. Exclusion Criteria, 6.8.1. Medication Not Permitted During the Study	Changed time after dosing before vaccinations are permitted to 90 days.	Updated to be consistent with CDC guidelines on timing of approved COVID-19 vaccines.

Section # and Name	Description of Change	Brief Rationale
8.4.8. Local Injection Site Tolerability, 8.5.9. Adverse Events of Special Interest, 8.5.9.2. Injection Site Reactions, 10.5. Appendix 5: Local Injection Site Tolerability Assessment, 10.6. Appendix 6: Management of Local Injection Site Reactions and Systemic Symptoms (Anaphylaxis)	Added injection site reactions as an adverse event of special interest (AESI), and procedures for assessing local injection site tolerability. Added Appendices for local injection site tolerability assessment and management of local injection site reactions and systemic symptoms.	Added because of the addition of IM injections to the protocol.
Synopsis, 3. Objectives and Endpoints 9.1 Statistical Hypotheses, 9.4.3. Secondary Endpoints, 9.4.4. Exploratory Endpoints	Updated language of secondary pharmacokinetic (PK) endpoint, added occurrence of non-serious AEs through Week 12 and changed ECG endpoint to Week 12 for the Part A secondary safety objective. Moved the virology endpoint from Part A to a secondary endpoint. Added resistance endpoint. Updated statistical analyses sections to match changes.	Updated PK endpoint wording to generalize to Parts A and B. Added Week 12 non-serious AE endpoint and updated secondary ECG endpoint to match reporting as described in the protocol. Made Part A virology endpoint a secondary endpoint. Added a resistance endpoint to monitor for potential development of resistance to VIR-7831.
Protocol Brief Title	Updated to add pharmacodynamics and add routes of study drug administration.	Updated brief study title to reflect addition of Part B.
8.11. Resistance Analyses	Added section for resistance surveillance.	Added to monitor for potential development of resistance to VIR-7831.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Removed home nursing option for study visits in Part A and specified that safety labs on Day 1 should be collected pre-dose. Clarified that screening procedures that are redundant with dosing procedures do not need to be performed twice if screening and dosing occur on the same day. Added AESI, disease-related events, and concomitant medication review to the Schedule of Activities. Clarified that phone call visits can be performed at site. Updated footnote numbering.	Updated Part A study procedures to remove home nursing option as all sites selected site visits. Clarified study procedures.
8.2.2. Physical examination, 8.4.2. Electrocardiograms	Clarified that screening procedures that are redundant with dosing procedures do not need to be performed twice if screening and dosing occur on the same day.	Clarified study procedures.
6.1. Study Intervention(s) Administered	Specified that the IV infusion duration for Part A is 1 hour and is 15 minutes for Part B. Added row to Table 4 to clarify infusion times.	Clarified infusion times for Part A and Part B.
6.8.1. Medication Not Permitted During the Study	Added that intravenous immunoglobulin (IVIG) is a not permitted during the study.	Added because a question was asked about IVIG in another study.
8.5.1. Time Period and Frequency for Collecting AE and SAE Information	Added AESI collection.	Clarification of AESI reporting.

Section # and Name	Description of Change	Brief Rationale
9.3. Analysis Sets, 9.3.1. Part A Analysis Sets, 9.3.2. Part B Analysis Sets	Added definition of Virology analysis set and clarified wording of Part A randomized Analysis set.	Updated to match statistical analysis plan.
9.4.4. Exploratory Endpoints	Added description of immunogenicity analyses.	Updated to provide details of analyses for exploratory endpoints.
8.3 Virologic Assessments	Section renamed from Exploratory Assessments to Virologic Assessments and subheading removed.	Updated section name because virology is no longer an exploratory assessment.
1.1. Synopsis, 2.1. Study Rationale; 2.3.2. Benefit Assessment, 2.3.3. Overall Benefit: Risk Conclusion; 4.3. Justification for Dose, 6.1. Study Interventions Administered	Added relevant information from the BLAZE-4, COMET-ICE, and ACTIV-3-TICO studies.	Updated to include the most recent available data from ongoing studies.
4.3. Justification for Dose	Added information from COMET-ICE, ACTIV-3-TICO, and resistance analyses and added information regarding IM injections.	Updated to include the most recent available data and provide information relevant to IM injections.
7.1. Discontinuation of Study intervention, 7.1.1. Temporary Discontinuation	Specified which discontinuation procedures are specific to IV infusion.	Clarification of which procedures are specific to IV administration.
5.4. Screen Failures	Clarified that re-screening will be permitted once during study conduct.	Clarification of study procedures
Synopsis, 4.1. Overall Design, 8.2. Screening Period	Changed wording for screening period from ’24 hours’ to ‘1 day’ prior to dosing.	Updated for consistency with the Schedule of Activities

Section # and Name	Description of Change	Brief Rationale
2.2. Background	Updated number of COVID-19 cases and deaths. Updated fatality estimates.	Updated to include most recent COVID-19 data. Removed European Centre for Disease Prevention and Control statistics because the Johns Hopkins COVID-19 tracker includes global data that are more recently updated.
2.2. Background, 2.3.2. Benefit Assessment	Added bamlanivimab/etesevimab to monoclonal antibodies that have received Emergency Use Authorization in the US.	Updated to include the most current available treatment options.
8.5.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Specified that disease-related events should be recorded in the specific eCRF and reported through Week 24 (EOS).	Clarification of the reporting method for disease-related events.
10.7. Appendix 7: Country-specific Requirements	Added Appendix.	Added to address requirements specific to South Korea.
2.3.1 Risk Assessment, 8.5.9.3. Immunogenicity, 8.5.9.4. Antibody-Dependent Enhancement,	Removed mention of approximate number of half-lives.	Removed extraneous information.
10.8. Appendix 8: Abbreviations and Trademarks, 11. References	Added and removed references and abbreviations as applicable to changes made in the protocol. Updated references for accuracy and consistent formatting.	Updated to match changes in the protocol text and for accuracy/consistency.
All sections	Other minor grammatical and typographical corrections.	To improve readability.

Amendment 01: (19-JAN-2021)

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

Overall Rationale for the Amendment

Protocol changes have been made to include nasal mid-turbinate swabs and resistance testing at the request of regulatory agencies.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Section 3 Objectives/Endpoints, Section 8.3.1 Virologic Measures, and, 9.4.4 Exploratory Endpoints	Nasal mid-turbinate swab added to exploratory endpoint.	At the request of regulatory agencies.
1.3 Schedule of Activities	Nasal mid-turbinate swab added to activities.	At the request of regulatory agencies.
2.2 Background	Included Emergency Use Authorization (EUA) for Regeneron mAbs.	Updated to include the most current available treatment options.
2.3.2 Benefit Assessment, and 2.3.3 Overall Benefit	IDMC data review from COMET-ICE added.	Updated to include the most recent available data from ongoing studies.
6.8.2 Permitted Concomitant Medications	Language included to permit use of COVID-19 vaccines following 90 days post dosing.	Updated to align with other studies in the program to the timing of approved COVID-19 vaccines.
8.3.1 Virologic Measures	Included language for the purpose of resistance surveillance analysis, next generation sequencing analysis of the spike protein of SARS-CoV-2 will be performed.	At the request of regulatory agencies.

Section # and Name	Description of Change	Brief Rationale
8.5.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Updated to clarify the collection of disease related events.	Clarification of previous text.

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