Protocol Amendment 2

Study ID: 214367

Official Title of Study: A Phase II/III randomized, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients.

NCT ID: NCT04545060

Date of Document: 17-JUN-2021

CLINICAL STUDY PROTOCOL

Study Title:	A Phase II/III randomized, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients
Sponsor:	This study is sponsored by Vir Biotechnology, Inc. GlaxoSmithKline is supporting Vir Biotechnology, Inc. in the conduct of this study. Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA
Investigational Product:	VIR-7831 (GSK4182136)
Regulatory Identifying Numbers:	**IND:** IND #149315 **EudraCT:** 2020-002871-36 **NCT:** NCT04545060
IND Number:	149315
Indication:	Treatment and prevention of coronavirus disease 2019(COVID-19)
Study Number:	VIR-7831-5001 (GSK Study 214367)
PPD :	Name: PPD Telephone: PPD Email: PPD
Medical Monitor:	Name: PPD Telephone: PPD Email: PPD
Protocol Version/Date:	Amendment 2: 17 June 2021

CONFIDENTIALITY STATEMENT

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PPD

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INVESTIGATOR SIGNATURE PAGE

VIR BIOTECHNOLOGY, INC

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STUDY ACKNOWLEDGMENT

A randomized, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients

VIR-7831-5001, Protocol Amendment 2, 17 June 2021

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

PPD, Pharm D
Vir PPD, Clinical Research — *{See Appended Electronic Signature Page}*

Printed Name | **Signature and Date**

INVESTIGATOR STATEMENT

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

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

Principal Investigator Printed Name | **Signature**

Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title: A randomized, multi-center, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients

Rationale:

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

Vir Biotechnology, Inc. (Vir) has developed a fully human neutralizing anti-SARS-CoV-2 antibody (Pinto et al. 2020), VIR-7831 (GSK4182136), which has an Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa (Hope et al. 2019) and increase half-life (Ko et al. 2014).

The Lead-In phase of this study will serve as the first-in-human (FIH) assessment and includes participants with mild/moderate COVID-19 to assess the safety and tolerability of VIR-7831. Following initial safety assessment in the Lead-In phase, assessment of safety and efficacy will commence in the Expansion phase of this study with the aim of preventing disease progression in high-risk participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19	Proportion of participants who have progression of COVID-19 through Day 29 as defined by: 1. Hospitalization > 24 hours for acute management of illness OR 2. Death
Secondary	
Safety Determine the safety and tolerability of VIR-7831 compared to placebo	• Occurrence of adverse events (AEs) • Occurrence of serious adverse events (SAEs) • Occurrence of adverse events of special interest (AESI)

Objectives	Endpoints
Assess the immunogenicity of VIR-7831	• Incidence and titers (if applicable) of serum ADA to VIR-7831
Pharmacokinetics Assess the pharmacokinetics (PK) of VIR-7831 in serum	• VIR-7831 pharmacokinetics (PK) in serum
Efficacy Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19	Proportion of participants who have progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR • Hospitalization for acute management of illness OR • Death
Evaluate the impact of VIR-7831 versus placebo on the duration and the severity of COVID-19 clinical symptoms	• Mean change in FLU-PRO Plus total score comparing Vir-7831 vs. Placebo (AUC through Day 7) • Time to symptom alleviation using the FLU-PRO Plus
Evaluate the efficacy of VIR-7831 versus placebo in reducing SARS-CoV-2 viral load	• Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8
Evaluate the efficacy of VIR-7831 against versus placebo in preventing COVID-19 respiratory disease progression	• Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifest by requirement for and method of supplemental oxygen at Day 8, Day 15, Day 22, or Day 29
Evaluate the efficacy of VIR-7831 versus placebo in preventing mortality	• 29-day, 60-day, and 90-day all-cause mortality
Exploratory	
Evaluate the impact of VIR-7831 versus placebo on incidence and duration of time on a ventilator, ICU length of stay (LOS), and total hospital LOS	• Total number of ventilator days from randomization through 90 days • Total intensive care LOS • Total hospital LOS
Evaluate the efficacy of VIR-7831 versus placebo in preventing hospitalization from	• Proportion of participants hospitalized due to non-respiratory

Objectives	Endpoints
non-respiratory complications of COVID-19	complications of COVID-19 (cardiac, renal, neurologic, hematologic events) by Day 8, Day 15, Day 22, and Day 29
Monitor on-treatment emergence of SARS-CoV-2 resistant mutants against VIR-7831	• Emergence of viral resistance mutants to mAb by SARS-CoV-2
Evaluate the efficacy of VIR-7831 versus placebo in reducing duration of SARS-CoV-2 viral shedding and viremia	• Detection of SARS-CoV-2 in nasal secretions by RT-PCR at baseline and during follow-up period through Day 29 • Detection of SARS-CoV-2 in blood by RT-PCR at baseline and during follow-up period through Day 29
Evaluate the efficacy of VIR-7831 versus placebo in reducing SARS-CoV-2 viral load	• Change from baseline in viral load in nasal secretions by qRT-PCR during follow-up period through Day 29
Evaluate the incidence of respiratory co-infection with SARS-CoV-2	• Respiratory pathogen detection in nasal secretions by PCR on Day 1
Evaluate the effect of VIR-7831 versus placebo on potential biomarkers of host response to SARS-CoV-2	• Evaluation of host immune responses and exploratory biomarkers related to SARS-CoV-2 and/or VIR-7831, including genetic, cellular, transcriptomic, and proteomic parameters
Measure the impact of VIR-7831 treatment on health-related quality of life and time away from work due to COVID19	• Change from baseline in Work Productivity and Activity Impairment (WPAI) questionnaire • Change from baseline for health-related quality of life according to the SF-12 hybrid questionnaire
Evaluate the impact of VIR-7831 versus placebo on the duration and the severity of COVID-19 clinical symptoms	• Mean change in FLU-PRO Plus total score (AUC through Days 14, 21) and Domain scores (AUC through Days 7, 14, 21) comparing Vir-7831 vs. Placebo • The proportion of participants with symptom alleviation using the FLU-PRO Plus at Days 7, 14, 21

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Overall Design:

This study is a randomized, double-blind, multi-center, placebo-controlled trial of VIR-7831, a monoclonal antibody (mAb) against SARS-CoV-2 for the prevention of progression of mild/moderate COVID-19 in high risk adult participants, with interim monitoring to allow early stopping for futility, efficacy, or safety. Participants with early, mild/moderate COVID-19 who are at high risk for progression of disease will be randomized 1:1 to receive a single, intravenous infusion of either VIR-7831 or equal volume saline placebo. Comparisons of safety and efficacy will be based on data from concurrently randomized participants.

Screening assessments will be performed within 24 hours before the first dose. Eligible participants will be treated in a blinded manner with a single IV dose on Day 1 and followed up to 24 weeks.

The Lead-In phase of this study will serve as the first-in-human assessment and will include 20 non-hospitalized participants who have early, mild/moderate COVID-19 and are at high risk of disease progression. These participants will be given a single intravenous infusion of VIR-7831 and confined for 7 days for safety monitoring. Following a safety assessment of unblinded data by an IDMC, the Expansion phase will progress, where additional participants with early, mild/moderate COVID-19 and who are at high risk of disease progression will be enrolled.

Brief Summary:

Lead-In Phase

The Lead-In phase of the study will evaluate the safety and tolerability of VIR-7831 in participants with early, mild/moderate COVID-19 who are at high risk of progression to severe disease. This phase will enroll approximately 10 participants in the active arm and 10 participants in the placebo arm. Participants will be monitored in an in-patient setting for a minimum of 7 days including assessments of respiratory status, oxygenation and other vital signs and laboratory evaluations. At the end of 7 days they will either be discharged to home or be formally hospitalized based on investigator assessment of clinical status. Subjects may be hospitalized or moved to a higher level of care, earlier than 7 days, at the investigator's discretion.

The first two eligible participants enrolled will be randomized 1:1 to VIR-7831 or placebo. These sentinel participants will be dosed and monitored for at least 48 hours post-dose and if the investigator has no immediate safety concerns, the remainder of the participants in the Lead-In phase will be dosed (total of 10 per arm inclusive of the sentinel participants). Participants will be stratified by age (≤70 vs. >70 years old) and symptom duration (≤3 days vs. 4-5 days).

During dose administration vital signs will be monitored every 15 minutes over the 1-hour IV infusion. Vital signs will also be monitored every hour after infusion for 2 hours and again at 6 hours after infusion. Vital signs, ECG, symptom-directed physical examinations(s), and AEs will be reviewed by the investigator. After discharge on Day 8, participants will be actively monitored by daily telephone calls (except on in-clinic visit days) through Day 15 for AEs and worsening of COVID-19.

Starting at Week 8, participants will be monitored monthly via phone call to assess for the incidence and of severity of subsequent COVID-19 illness, if any, for a total of 24 weeks from dosing.

Timing of visits and frequency of assessments are outlined in the Schedule of Activities, Section 1.3.

Intensive PK and Immunogenicity Sub-study

All 20 participants enrolled in the Lead-In (N=10 per arm; VIR-7831 or placebo) will be assigned to an immunogenicity sub-study and have additional timepoints for PK blood sampling. Serum PK and anti-drug antibodies (ADA) samples will be collected as detailed in the Schedule of Activities (Section 1.3, Table 1).

Expansion Phase

The Expansion phase of the study will progress following assessment of available unblinded safety data from the Lead-in phase (N=10 per arm through Day 15 of follow-up) by an IDMC. Outpatient participants with early mild/moderate COVID-19 who are at high risk for progression to severe disease will be randomized in a 1:1 ratio to receive a single IV infusion of VIR-7831 or placebo.

Participants will be monitored through at least 2 hours post-dose prior to discharge from the study unit. During dose administration vital signs will be monitored every 15 minutes over the 1-hour IV infusion. Vital signs will also be monitored every hour after infusion for 2 hours. Participants will subsequently be actively monitored on an outpatient basis with in-person study visits at Weeks 1, 2, 3, and 4 and daily telephone calls (except on in-clinic visit days) through Day 15 for AEs and worsening of COVID-19. Serum PK and anti-drug antibodies (ADA) samples will be collected as detailed in the Schedule of Activities (Section 1.3, Table 2).

Starting at Week 8, participants will be monitored monthly via phone call to assess for the incidence and of severity of subsequent COVID-19 illness, if any, for a total of 24 weeks from dosing.

Immunology Assessment Sub-study

Participants in the Lead-In phase will have blood collections for the isolation of peripheral blood mononuclear cells (PBMCs) as part of the required sub-study to explore the host immune response and potential biomarkers of infection.

At select participating sites in the Expansion Phase, participants may consent to an optional sub-study. Subjects who consent to the optional sub-study will have blood collection for the isolation of PBMCs.

The timepoints for blood collection for the sub-study are outlined in the Schedule of Activities (Section 1.3, Table 2). The sub-study will be done at selected sites in the United States only. All 20 subjects in the Lead-In Phase will participate in the sub-study. Approximately, 40-100 participants will be enrolled in the optional sub-study in the Expansion Phase.

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Number of Participants:

Lead-In Phase

Approximately 10 participants in the placebo arm and approximately 10 participants in the treatment arm.

Expansion Phase

Approximately 670 participants in the placebo arm and approximately 670 participants in the treatment arm.

Intervention Groups and Duration:

Screening assessments will be performed within 24 hours prior to randomization. Eligible participants will be treated in a blinded manner with a single IV dose on Day 1 and followed up to 24 weeks.

In the Lead-In phase, 20 outpatient participants with mild/moderate COVID-19 will be randomized 1:1 to receive a single IV dose of VIR-7831 or placebo. Participants will be stratified by age (≤70 vs. >70 years old) and symptom duration (≤3 days vs. 4-5 days). Participants enrolled in the Lead-In phase of the study will be closely monitored in an in-patient setting for a minimum of 7 days. At the end of 7 days they will either be discharged to home or be formally hospitalized based on investigator assessment of clinical status. Subjects may be hospitalized or moved to a higher level of care, earlier than 7 days, at the investigator's discretion.

In the Expansion phase, participants with mild/moderate COVID-19 will be randomized 1:1 to receive a single IV dose of VIR-7831 or placebo.

Participants in the Expansion phase will be stratified by the following criteria:

1. Age: ≤70 vs. >70 years old
2. Duration of COVID-19 symptoms: ≤3 days vs. 4-5 days

In addition, randomization will be stratified by region of the world to protect against imbalances within specific regions which may have different standards of care.

Independent Data Monitoring Committee (IDMC)

An IDMC will actively monitor interim unblinded safety (Lead-In phase) and interim unblinded safety and efficacy data (Expansion phase) to make recommendations to Vir regarding ongoing study conduct as detailed in the IDMC Charter. The IDMC members will include physicians with relevant medical training and one statistician. As noted above, the IDMC will review unblinded safety data from the Lead-In phase of the study prior to initiation of the Expansion phase. In addition, the IDMC will perform regular safety reviews during the Expansion phase.

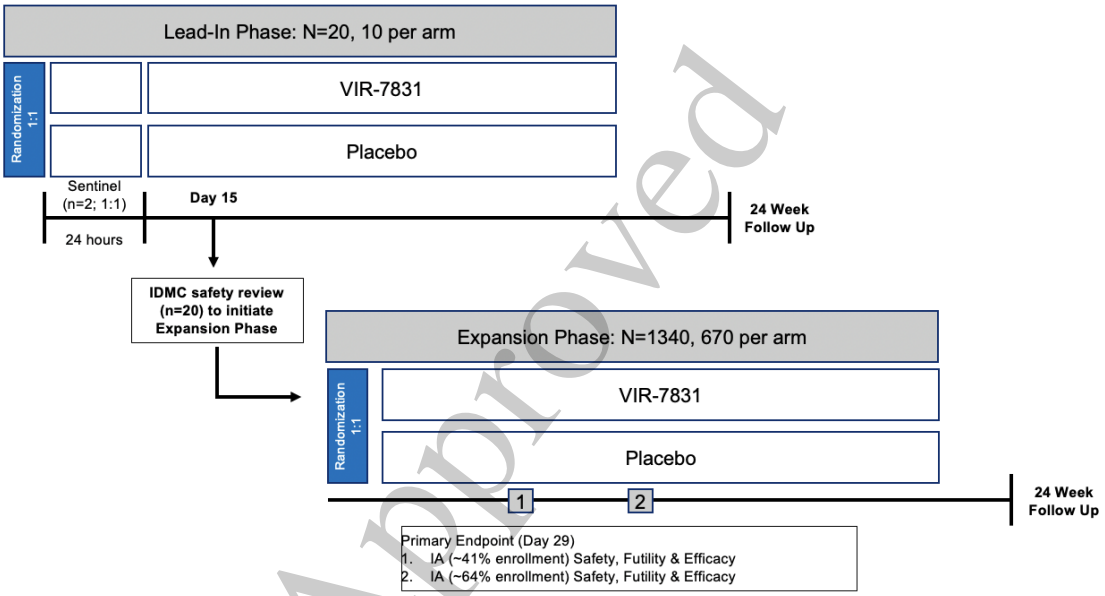
The first safety review in the Expansion phase will include available safety and tolerability data though Day 15 from a total of 60 participants (30 per arm). If deemed necessary, an additional safety review will be conducted after approximately 100 additional participants are enrolled (50 per arm) to review safety and tolerability data through Day 15. IDMC members will also review all SAEs via draft CIOMS when they become available. Finally, two interim analyses (IA) will be conducted at approximately

41% of participants enrolled and approximately 64% of participants enrolled to evaluate safety, futility, and efficacy based on data through Day 29 for these participants. Additional details regarding the IDMC process will be available in relevant IDMC documents.

Joint Safety Review Team (JSRT)

A Joint Safety Review Team (JSRT) comprised of team members from clinical research, pharmacovigilance and statistics will determine if a safety concern identified during instream blinded data review needs to be escalated to the IDMC. The IDMC will act in accordance with the process defined in the IDMC Charter.

1.2. Study Schema



1.3. Schedule of Activities

Table 1: Lead-In Phase: Schedule of Activities

Study Stage	Screening	In-patient				Follow-up Period									
Study Visit Week						W2		W3	W4	W6	W8	W12	W16[h]	W20	W24 (EOS/EW)
Study Visit Day ± Visit Window	D-1	D1	D2	D5	D8	D11	D15±1	D22±1	D29±2	D43±3	D57±4	D85±7	D113±7	D141±7	D169±7
Informed consent	X														
Demography	X														
Medical history	X														
Inclusion/exclusion criteria	X														
Physical examination[a]	X[a]	X[a] (daily)					X[a]	X[a]	X[a]						
Body weight & height	X														
Vital signs [b] (including O2 saturation)	X	X[b]	X (every 8 hrs)				X	X	X						X
Local safety lab assessments	X	X[j]	X[j]	X	X										
Laboratory assessments (central)		X[d]	X	X	X		X	X	X						
SARS-CoV-2 diagnostic test [i] (point-of-care or local laboratory test)	X[i]														
Pregnancy test	X														X
Electrocardiogram	X	X (daily)													
Randomization		X													
Study drug administration		X													
Blood sample for PK analysis		X[c]	X	X	X		X		X	X	X	X		X	X
Blood sample for anti-drug antibody		X[d]							X			X		X	X
Blood sample for anti-SARS-CoV-2 antibody		X[d]			X		X		X			X			X

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Table 1: Lead-In Phase: Schedule of Activities (Continued)

Study Stage	Screening	In-patient						Follow-up Period							
Study Visit Week						W2		W3	W4	W6	W8	W12	W16[h]	W20	W24 (EOS/EW)
Study Visit Day ± Visit Window	D-1	D1	D2	D5	D8	D11	D15±1	D22±1	D29±2	D43±3	D57±4	D85±7	D113±7	D141±7	D169±7
Blood sample for virology		X[d]			X		X		X						
Blood sample for FcR and IgG analysis (optional test)		X[d]													
Blood sample for RNA Paxgene (optional test)		X[d]			X										
Nasopharyngeal swab for virology		X[d]		X	X	X	X	X	X[g]						
Symptom self-assessment (Flu-PRO Plus)		X (daily through Day 21)							X		X	X			
Phone call for active COVID-19 monitoring[e]					X (daily)[e]										
Phone call for subsequent COVID-19 illness											X	X	X	X	
Review/record AEs [f]	X[f]														
Concomitant medications	X														
Blood sample for exploratory immunology		X[d]			X										
PBMC sample for immunology		X[d]							X						X

[a] Complete physical examination should be performed on Day 1; all other visits should be symptom-directed physical examinations
[b] Vital signs on Day 1 should be recorded prior to dose administration, every 15 min during IV infusion, and at 1, 2 and 6 hours after end of infusion.
[c] On Day 1, sample collection will occur pre-dose and at the end of infusion, 1, 2, 6, and 12 hours following end of infusion
[d] On Day 1, sample collection will occur pre-dose
[e] Daily starting on Day 9, no phone call conducted on in-clinic visit days
[f] Adverse events will be assessed up to Week 12. Serious adverse events (SAEs) will be assessed up to Week 24
[g] If nasopharyngeal swab sample is positive for SARS-CoV-2 by RT-PCR at Week 4 additional nasopharyngeal swab samples may be collected up to Week 24
[h] Week 16 is planned as site phone call to participants only
[i] Participants may be tested at screening if symptom onset ≤ 5 days
[j] Urine for albumin to creatinine ratio should be collected pre-dose on Day 1 and on Day 2 and performed locally

Table 2: Expansion Phase: Schedule of Activities

Study Stage	**Screening**	**Dosing**	**Follow-up Period**										
Study Visit Week		**W1**			**W2**		**W3**	**W4**	**W8[i]**	**W12**	**W16[i]**	**W20**	**W24 (EOS/EW)**
Study Visit Day ± Visit Window	**D -1**	**D1**	**D5**	**D8±1**	**D11±1**	**D15±1**	**D22±1**	**D29±2**	**D57±4**	**D85±7**	**D113±7**	**D141±7**	**D169±7**
Informed consent	X												
Demography	X												
Medical history	X												
Inclusion/exclusion criteria	X												
Physical examination[a]	X[a]	X[a]		X[a]		X[a]	X[a]	X[a]					
Body weight & height	X												
Vital signs (including O2 saturation)	X	X[b]		X		X	X	X					X
Local safety lab assessments	X[k]												
Laboratory assessments (central)		X[d]		X		X	X	X					
SARS-CoV-2 diagnostic test [j] (point-of-care or local laboratory test)	X[j]												
Pregnancy test	X												X
Electrocardiogram (Pre-dose)		X											
Phone call for active COVID-19 monitoring[e]		X (daily)[e]											
Randomization		X											
Study drug administration		X											
Blood sample for PK analysis		X[c]		X		X		X		X		X	X
Blood sample for anti-drug antibody		X[d]						X		X		X	X
Blood sample for anti-SARS-CoV-2 antibody		X[d]		X		X		X		X			X
Blood sample for virology		X[d]		X		X		X					

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Table 2: Expansion Phase: Schedule of Activities (Continued)

Study Stage	Screening	Dosing	Follow-up Period										
Study Visit Week		**W1**			**W2**		**W3**	**W4**	**W8[i]**	**W12**	**W16[i]**	**W20**	**W24 (EOS/EW)**
Study Visit Day ± Visit Window	**D -1**	**D1**	**D5**	**D8±1**	**D11±1**	**D15±1**	**D22±1**	**D29±2**	**D57±4**	**D85±7**	**D113±7**	**D141±7**	**D169±7**
Blood sample for FcR and IgG analysis (optional test)		X[d]											
Blood sample for RNA Paxgene (optional test)		X[d]		X									
Nasopharyngeal swab for virology		X[d]	X	X	X	X	X	X[h]					
Symptom self-assessment (Flu-PRO Plus)		X (daily through Day 21)						X	X	X			
WPAI Questionnaire		X				X		X	X	X	X	X	X
SF-12 Hybrid Questionnaire		X				X		X	X	X	X	X	X
Long COVID assessment													X
Phone call for subsequent COVID19 illness									X	X	X	X	
Review/record AEs [f]	X[f]												
Concomitant medications	X												
Blood sample for exploratory immunology		X[d]		X									
PBMC sample for immunology [g]		X[d]						X					X

[a] Complete physical examination should be performed on Day 1; all other visits should be symptom-directed physical examinations
[b] Vital signs on Day 1 should be recorded prior to dose administration, every 15 min during IV infusion of study drug, and at 1 and 2 hours after infusion
[c] On Day 1, sample will be collected pre-dose and at the end of infusion
[d] On Day 1, sample collection will occur pre-dose
[e] No phone call conducted on in-clinic visit days
[f] Adverse events will be assessed up to Week 12 post dose. Serious adverse events (SAEs) will be assessed up to Week 24.
[g] Optional immunology sub-study
[h] If nasopharyngeal swab sample is positive for SARS-CoV-2 by RT-PCR at Week 4 additional nasopharyngeal swab samples may be collected up to Week 24
[i] Week 8 and Week 16 are planned as site phone call to participants only
[j] Participants may be tested at screening if symptom onset ≤ 5 days
[k] Except for ABO typing, all other local lab assessments may be performed or not as determined necessary by the investigator or required by local regulations

2. INTRODUCTION

2.1. Study Rationale

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

After the first four months of the COVID-19 pandemic, a number of risk factors associated with worse clinical disease were identified. Older age and patients with co-morbidities were more likely to have severe disease requiring hospitalization or die. Therefore, this study will enroll adults at high risk of medical complications from COVID-19, including but not limited to older adults (age ≥ 55 years) and individuals aged ≥ 18 years with comorbidities associated with worse outcomes, including diabetes, obesity (BMI > 30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate to severe asthma (Garg 2020; Petrilli 2020).

A placebo control is required to distinguish the safety and tolerability of VIR-7831 from the background signs and symptoms of COVID-19 and to evaluate its potential benefit on clinical outcomes. The use of a placebo arm allows for a valid evaluation of any changes in efficacy and safety attributable to VIR-7831 versus those attributable to background supportive care given during the study.

2.2. Background

A novel betacoronavirus was first reported in December 2019 causing severe pneumonia in Wuhan, China. Since that time, SARS-CoV-2 has spread throughout the world leading to over 16 million confirmed cases and over 650,000 deaths as of July 27, 2020 (COVID-19 dashboard, Johns Hopkins). There is an urgent need for effective treatment throughout the course of illness. Emerging data suggest that morbidity and mortality associated with COVID-19 exceeds that of influenza and is impacted by age as well as underlying comorbidities that place certain groups at higher risk of poor outcomes. Current estimates of overall case fatality rates range from 1.8 to 3.4% with mortality rates exceeding 25% for some populations (Ferguson 2020; Bialek 2020). Based on current experience in China, the UK, and Italy, experts have estimated that approximately 30% of those who are hospitalized will require critical care and that 50% of those in critical care will die. In addition, an age-dependent proportion of those that do not require critical care will also die (Ferguson 2020). Mortality rates are likely to be impacted by access to appropriate care as intensive care unit (ICU) beds and critical care capacity becomes overwhelmed. Not only is there a high unmet need for treatment of those with severe disease but also for therapies designed to prevent the progression of disease in those with early infection. Currently available data suggest that SARS-CoV-2 is associated with a

relatively long incubation period, with mean incubation period from exposure to symptomatic disease of approximately 5 days with the 95% percentile of the distribution at 12.5 days (Li 2020). The median time to progression to severe disease (ICU admission/development of ARDS) from onset-of-symptoms has been estimated to be 12 days (range 8 to 15 days) with a median duration from onset to death or discharge of 21 days (range 17 to 25 days) (Zhou 2020). In addition, viral loads are highest early in the course of disease and tend to fall once severe sequelae have ensued, although remain detectable by RT-PCR well into the course of disease (Zou 2020; Wölfel 2020). Notably, although viral nucleic acid was detected well after symptom resolution in participants with mild infection, shedding of infectious virus in sputum was limited to the first week of symptoms (Wölfel 2020). These data suggest that early intervention with a potently neutralizing antibody prior to the onset of severe sequelae of disease may effectively prevent disease progression and hasten the resolution of disease. Experience with the use of neutralizing mAbs in the treatment of uncomplicated acute influenza support the idea that the time to intervention may be a key determinant of clinical success. Studies that enrolled participants within ≤ 5 days (Ali 2018) or < 72 hours (Hershberger 2019) of symptom onset were unable to demonstrate statistically significant faster time to resolution of symptoms, whereas a study that enrolled patients with symptom onset no greater than 48 hours prior to treatment demonstrated statistically significant reductions in time to resolution of symptoms (~2 day reduction compared to the placebo group) (Yang 2019).

Given these factors, a highly potent neutralizing mAb against SARS-CoV2 administered prior to progression to severe disease could prevent progression and lead to faster resolution of symptoms.

Vir Biotechnology, Inc. (Vir) has developed a fully human neutralizing anti-SARS-CoV-2 antibody, VIR-7831 (GSK4182136), which contains a 2 amino acid Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. VIR-7831 binds to a conserved epitope on the SARS-CoV and SARS-CoV-2 spike protein and has been shown to neutralize pseudovirus and live virus in several independent laboratories (Pinto D et al. 2020).

2.3. Benefit/Risk Assessment

Information about the reasonably expected adverse events of VIR-7831 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: VIR-7831		
Infusion reactions including hypersensitivity reactions (HSR)	While VIR-7831 is a fully human IgG, infusion-related reactions (IRR) 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 monoclonal antibodies or any of the excipients present in the investigational product. **Monitoring**: • 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. **Mitigation**: • In the sentinel participants and Lead-In phase of the FIH study, vital sign measurement will be conducted every 15 minutes during the planned 1-hour IV infusion and at 1, 2, and 6 hours post-infusion. In the Expansion phase, vital signs will be monitored every 15 minutes over the 1-hour IV infusion and at every hour after infusion for 2 hours. • Infusion related reactions are categorized as AESIs

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Investigators will be provided with general guidance on management of 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. • Investigators will be instructed to discontinue IV infusions for participants who develop Grade 3 or higher infusion reactions. • If a participant experiences a Grade 2 IRR, investigators will be instructed to pause the infusion. The infusion may subsequently resume at a slower pace of infusion, at the investigator's discretion, and/or after symptomatic treatment (e.g., anti-histamines, IV fluids). • IV infusion will be administered in the clinic with staff trained in emergency care & resuscitation procedures & emergency care kit on hand during treatment & post therapy observation periods.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunogenicity	While VIR-7831 is a fully human IgG, the development of anti-drug antibodies (ADA) that have the potential to impact safety and/or efficacy are a potential general risk associated with the mAb class of therapeutics	This study will include participant follow-up for a period of 24 Weeks (estimated 5 half-lives) to assess for the potential of immunogenicity (measurement of ADA) as well as if ADA is potentially causally associated with specific safety concerns and/or impact efficacy
Antibody Dependent Enhancement (ADE) due to sub-neutralizing levels of VIR-7831 enhancing fusion or leading to FcγR mediated increased viral uptake and replication with virus production	This is a concern related to the potential for participants with sub-neutralizing mAb levels to experience a higher incidence of infection and/or more severe disease compared to participants with no circulating mAb and/or established protective immunity to SARS-CoV-2. ADE associated with Dengue virus 1-4 serotype infections is one of the most widely cited examples in which reinfection with a different serotype can, in a minority of 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 FcR-expressing cells, such as macrophages, and increased viral replication in these cells. Recent data shows that SARS-CoV-2 does not replicate efficiently in macrophages [Hui 2020], suggesting minimal to no risk of ADE via this mechanism.	**Monitoring:** • This study will include participant follow up for a period of 24 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 (initial or re-infection in the case of prevention and treatment, respectively) as well as the severity of disease will be performed by the IDMC to assess for imbalances between mAb- and placebo-treated participants. **Mitigation:** • Futility and safety criteria are built into the study design to permit early stopping of the study for an imbalance in incidence (initial or re-infection in the case of prevention and treatment, respectively) or severity of disease for this study (see Section 10.1.5 for more details on the IDMC).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ADE due to enhanced disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs	There is the possibility that a large amount of antibody that binds, but does not neutralize, virus in the presence of a high viral load could result in immune complex deposition and complement activation in tissue sites of high viral replication, such as the lungs, vascular endothelia, renal or cardiovascular tissue [Hamming 2004], leading to tissue damage/immune complex disease This is hypothesized to have contributed to inflammation and airway obstruction observed in the small airways of infants who received a formalin-inactivated (FI) respiratory syncytial virus (RSV) vaccine [Polack 2002] and in a few cases of fatal H1N1 influenza infection [Wu 2010] The potential for enhanced disease in this setting may be due to low affinity or cross-reactive antibodies with poor or no neutralizing activity Triggering of cytokine release by antibody-virus-FcγR interactions although usually highly beneficial due to their direct antiviral effects and immune cell recruitment to control viral spread in tissues, also has the potential to enhance pathologic changes initiated by the viral infection Observational data from 5000 COVID-19 patients treated with convalescent plasma, although not placebo controlled, is suggestive that even polyclonal mixtures of neutralizing and non-neutralizing antibodies can be safely administered [Joyner 2020]	**Monitoring:** • In this study, periodic review of clinical signs and symptoms of COVID-19, clinical chemistry, adverse events, end-organ disease and histopathological diagnoses (as available per routine care) will be performed by the Joint Safety Review Team to identify potential cases of immune complex disease • Additional monitoring in the event a participant develops signs or symptoms of cardiac complications (See Section 8.3) • In addition, the IDMC will be instructed to perform periodic data review of clinical signs and symptoms of COVID-19, clinical chemistry, any cardiac assessments, end-organ disease and histopathological diagnoses (as available per routine care) with the aim of identifying imbalances in the study arms with respect to worsening of COVID-19-related end-organ complications that may reflect immune-complex reactions. • Assessments of the overall duration and severity of COVID-19 will be performed by the IDMC to assess for imbalances between mAb- and placebo-treated participants.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	VIR-7831 shows potent binding in vitro as well as neutralization of pseudovirus and live virus thus this risk is deemed to be low.	**Mitigation:** Futility and safety criteria are built into the study design to permit early stopping of the study for an imbalance in or severity of disease (see Section 10.1.5 for more details on the IDMC)
Study Procedures		
Infusion site reactions including hypersensitivity reactions	While VIR-7831 is a fully human IgG, infusion-related reactions (IRR) 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 monoclonal antibodies or any of the excipients present in the investigational product. **Monitoring:** • 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. • For the Lead-In phase of this study, vital sign measurements will be conducted every 15 minutes during the planned 1-hour IV infusion and at 1, 2, and 6 hours post-infusion. For the Expansion phase, vital signs will be monitored every 15 minutes over the 1-hour IV infusion and at every hour after infusion for 2 hours.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Infusion time can be extended at the discretion of the Investigator, Sponsor or IDMC based on local infusion-related symptoms or other safety findings. • Joint Safety Review Team reviews will be conducted at least every two weeks to determine if a significant safety signal of severe hypersensitivity reaction is identified. The IDMC will be notified per Charter for adjudication. **Mitigation**: • Investigators will be instructed to discontinue IV infusions for participants who develop Grade 3 or higher infusion reactions using *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 investigator's discretion, and/or after symptomatic treatment (e.g. anti-histamines, IV fluids). • Investigators will be provided with general guidance on management of 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.

VIR-7831
VIR-7831-5001(GSK Study 214367)

2.3.2. Benefit Assessment

Although VIR-7831 has not been studied before in this acutely ill population, there is biologic rationale which supports the use of VIR-7831, an antiviral mAb in the early treatment of COVID-19 to prevent progression.

VIR-7831 has been demonstrated in vitro to be a highly potent fully human IgG neutralizing SARS-CoV-2 antibody which has the potential to be an effective therapeutic in mild to critically ill patients with COVID-19. VIR-7831 does not bind to normal human tissues in the tissue cross-reactivity study and there were no adverse findings after 2 weeks in the 2-week repeat dose monkey toxicity study. The no-observed-adverse-effect-level (NOAEL) in the monkey study was 500 mg/kg, the highest dose tested.

The study population to be enrolled in this study has a high unmet medical need. VIR-7831 may or may not improve the time to clinical response or overall clinical outcome in an individual participant with mild or 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 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.

Based on the high unmet medical need and considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with VIR-7831 are justified by the anticipated benefits that may be afforded to participants with mild to moderate COVID-19.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19	• Proportion of participants who have progression of COVID-19 through Day 29 as defined by: 1. Hospitalization > 24 hours for acute management of illness OR 2. Death
Secondary	
Safety • Determine the safety and tolerability of VIR-7831 compared to placebo	• Occurrence of adverse events (AEs) • Occurrence of serious adverse events (SAEs) • Occurrence of adverse events of special interest (AESI)
• Assess the immunogenicity of VIR-7831	• Incidence and titers (if applicable) of serum ADA to VIR-7831
Pharmacokinetics • Assess the pharmacokinetics (PK) of VIR-7831 in serum	• VIR-7831 pharmacokinetics (PK) in serum
Efficacy • Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19	Proportion of participants who have progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR • Hospitalization for acute management of illness OR • Death
• Evaluate the impact of VIR-7831 versus placebo on the duration and the severity of COVID-19 clinical symptoms	• Mean change in FLU-PRO Plus total score comparing Vir-7831 vs. Placebo (AUC through Day 7) • Time to symptom alleviation using the FLU-PRO Plus

• Evaluate the efficacy of VIR-7831 versus placebo in reducing SARS-CoV-2 viral load	• Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8
• Evaluate the efficacy of VIR-7831 against versus placebo in preventing COVID-19 respiratory disease progression	• Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifest by requirement for and method of supplemental oxygen at Day 8, Day 15, Day 22, or Day 29
• Evaluate the efficacy of VIR-7831 versus placebo in preventing mortality	• 29-day, 60-day, and 90-day all cause mortality
Exploratory	
• Evaluate the impact of VIR-7831 versus placebo on incidence and duration of time on a ventilator, ICU length of stay (LOS), and total hospital LOS	• Total number of ventilator days from randomization through 90 days • Total intensive care LOS • Total hospital LOS
• Evaluate the efficacy of VIR-7831 versus placebo in preventing hospitalization from non-respiratory complications of COVID-19	• Proportion of participants hospitalized due to non-respiratory complications of COVID-19 (cardiac, renal, neurologic, hematologic events) by Day 8, Day 15, Day 22, and Day 29
• Monitor on-treatment emergence of SARS-CoV-2 resistant mutants against VIR-7831	• Emergence of viral resistance mutants to mAb by SARS-CoV-2
• Evaluate the efficacy of VIR-7831 versus placebo in reducing duration of SARS-CoV-2 viral shedding and viremia	• Detection of SARS-CoV-2 in nasal secretions by RT-PCR at baseline and during follow-up period through Day 29 • Detection of SARS-CoV-2 in blood by RT-PCR at baseline and during follow-up period through Day 29
• Evaluate the efficacy of VIR-7831 versus placebo in reducing SARS-CoV-2 viral load	• Change from baseline in viral load in nasal secretions by qRT-PCR during follow-up period through Day 29
• Evaluate the incidence of respiratory co-infection with SARS-CoV-2	• Respiratory pathogen detection in nasal secretions by PCR on Day 1
• Evaluate the effect of VIR-7831 versus placebo on potential biomarkers of host response to SARS-CoV-2	• Evaluation of host immune responses and exploratory biomarkers related to SARS-CoV-2 and/or VIR-7831, including genetic, cellular, transcriptomic, and proteomic parameters

• Measure the impact of VIR-7831 treatment on health-related quality of life and time away from work due to COVID19	• Change from baseline in Work Productivity and Activity Impairment (WPAI) questionnaire • Change from baseline for health-related quality of life according to the SF-12 hybrid questionnaire
• Evaluate the impact of VIR-7831 versus placebo on the duration and the severity of COVID-19 clinical symptoms	• Mean change in FLU-PRO Plus total score (AUC through Days 14, 21) and Domain scores (AUC through Days 7, 14, 21) comparing Vir-7831 vs. Placebo • The proportion of participants with symptom alleviation using the FLU-PRO Plus at Days 7, 14, 21

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, double-blind, multi-center, placebo-controlled trial of VIR-7831, a monoclonal antibody (mAb) against SARS-CoV-2 for the prevention of progression of mild/moderate COVID-19 in high risk participants, with interim monitoring to allow early stopping for futility, efficacy, or safety. Participants with early, mild/moderate COVID-19 who are at high risk for progression of disease will be randomized 1:1 to receive a single, intravenous infusion of either VIR-7831 or equal volume saline placebo. Comparisons of safety and efficacy will be based on data from concurrently randomized participants.

Screening assessments will be performed within 24 hours before the first dose. Eligible participants will be treated in a blinded manner with a single IV dose on Day 1 and followed up to 24 weeks.

The Lead-In phase of this study will serve as the first-in-human assessment and will include 20 non-hospitalized participants who have early, mild/moderate COVID-19 and are at high risk of disease progression. These participants will be given a single intravenous infusion of VIR-7831 and confined for 7 days for safety monitoring. Following a safety assessment of unblinded data by an IDMC, the expansion phase will progress, where additional participants with early, mild/moderate COVID-19 and who are at high risk of disease progression will be enrolled.

4.2. Scientific Rationale for Study Design

This study is a two-phase (FIH to phase 2/3) randomized, placebo-controlled study to evaluate the safety, tolerability, PK, immunogenicity, and efficacy of VIR-7831 compared to placebo in the treatment of early mild/moderate COVID-19 in adults at high risk of medical complications from COVID-19, including but not limited to older adults (age ≥ 55 years) and all individuals age 18 or older with comorbidities associated with worse outcomes, including diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate to severe asthma. The study will include outpatients with SARS-CoV-2, the virus that causes COVID-19, as confirmed by local laboratory tests and/or point of care tests.

The study will include a Lead-In phase to assess the safety of VIR-7831 compared to placebo (10 participants per arm). A single dose level designed to provide potential therapeutic benefit will be studied and will be delivered via IV infusion. Participants will be admitted to a study unit and monitored closely for adverse events, changes in laboratory parameters and progression (or improvement) in disease signs and symptoms. This approach is appropriate given the theoretical risk for antibody dependent enhancement of disease, including immune complex formation and deposition in tissues, in patients with high viral burden [Liu 2019].

Following review of available unblinded safety data through Day 15 by the IDMC, the study will expand to enroll additional participants. The purpose of the Expansion phase will be to evaluate the safety and efficacy of VIR-7831 in comparison to the placebo control arm. Two interim analyses at approximately 41% of participants enrolled and

approximately 64% of participants enrolled will be conducted to evaluate futility, efficacy, and safety based on data through Day 29 for these participants. To date, there are no approved treatments for mild/moderate COVID-19. A placebo control is required to distinguish the safety and tolerability of VIR-7831 from the background signs and symptoms of COVID-19 and to evaluate its potential benefit on clinical outcomes. The use of a placebo arm allows for a valid evaluation of any changes in efficacy and safety attributable to VIR-7831 versus those attributable to background supportive care given during the study.

A double-blind design is a standard methodology for randomized, controlled studies to avoid bias. Unblinded safety and efficacy data will be reviewed regularly by an IDMC.

The primary endpoint to assess efficacy of treatment is progression of mild/moderate COVID-19 defined by hospitalization >24 hours for acute management of illness or death within 29 days of randomization. The transition from outpatient status without hypoxemia or oxygen requirement to hospitalization for acute care or death is a clinically significant milestone. It is considered to be clinically important to participants and physicians alike. A 29-day period to assess the primary endpoint is appropriate as the median time for COVID-19 related hospital admission has been reported to be 7-11 days and the median time to clinical deterioration, 9-12 days (Zhou 2020, Huang 2020).

The most significant of the secondary endpoints is evaluation of whether VIR-7831 can shorten the duration or lessen the severity of COVID-19. Demonstration of an improvement in the severity of disease following administration of VIR-7831 would be considered highly clinically meaningful. Other efficacy endpoints related to decrease in viral shedding, mortality, and health resource utilization – length of hospital stay, ICU stay, time ventilated – are also highly clinically relevant and recommended in COVID-19 trial guidelines (NICE 2020; WHO 2020; FDA 2020).

4.3. Justification for Dose

4.3.1. VIR-7831

A single dose of 500 mg was selected for the study based on in vitro neutralization data, in vitro resistance data, expected human PK extrapolated from a study in cynomolgus monkeys, and the results of the GLP monkey toxicology study.

VIR-7831 neutralized SARS-CoV-2 live virus with an average 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 even at the lowest dose tested (~10x EC_{50}), 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, modest fold changes in EC_{50} were observed during viral selection (5-to 6-fold change in EC_{50}) for some passages (PC-7831-0109). Sequencing and testing of spike variants from these passages using a pseudotyped virus system did not identify causal variants for this modest shift in potency. One passage of virus did demonstrate a >10 fold shift in EC_{50} which correlated with an E340A mutation. Further assessment has identified E340A to be a monoclonal antibody-resistant mutant (MARM) that confers a >100-fold reduction in susceptibility to VIR-7831. Notably, E340 is 100% conserved among available

SARS-CoV-2 sequences. Due to the binary nature of the resistance selection results, a specific inhibitory quotient (IQ) was not informed by the resistance profiling. However, as our understanding of the biology of SARS-CoV-2 is currently still limited and very few strains are available to directly assess breadth of coverage, a conservative IQ (>10) is appropriate in this case.

The cynomolgus monkey PK from study PK-7831-0115 was fit to a 2 compartment PK model. Human PK parameters were scaled from the cynomolgus monkey using an allometric scaling approach for fully human IgGs (allometric coefficient of 0.85 and 1 for CL and V, respectively; Deng 2011). The predicted serum clearance of VIR-7831 in humans is estimated to be 141 mL/day and estimated volume of distribution is 6500 mL (~93 mL/kg) assuming human weight of 70 kg. The projected human terminal elimination half-life is approximately 32 days.

In order to reduce risk to patients (treatment failure, resistance), the dose was selected to ensure that VIR-7831 concentrations in lung are maintained at or above levels anticipated to be protective of SARS-CoV-2 infection for the duration of the 28-day treatment window. A dose of 500 mg is expected to maintain serum levels at or above 38.5 µg/mL for the duration of the 28-day treatment period. 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 0.25-0.68 for whole lung and interstitial fluid, respectively; Baxter 1994, Covell 1986, Datta-Mannan 2019, Lobo 2004) the serum trough concentration following a 500 mg dose is expected to result in lung concentrations associated with maximal (> 99%) antiviral activity; > 29 x tissue-adjusted EC_{90} for the duration of the 28 day treatment period. This conservative inhibitory quotient (29) in lung is believed to be appropriate to increase potential for treatment success and reduce risk for resistance.

Additionally, a 500 mg dose is anticipated to result in protective levels of VIR-7831 in nasopharyngeal secretions (>5 x tissue adjusted EC_{90} assuming NPS:serum ratio of 0.05, Lim 2017) which could potentially reduce transmission.

The NOAEL for VIR-7831 was 500 mg/kg, the highest dose tested, when VIR-7831 was administered via IV infusion once a week for 2 weeks in cynomolgus monkeys (TX-7831-0102). At this NOAEL, preliminary C_{max} and AUC_{0-t} (AUC from time 0 to 168hr post-end of infusion following the 2nd dose) were 13500 µg/mL and 48200 µg•day/mL, respectively. The human equivalent dose (HED) (HED calculated via direct mg/kg conversion according to FDA guidance on proteins administered intravascularly with Mr > 100,000 daltons; FDA 2005) is 500 mg/kg or a 30,000 mg fixed dose (using human body weight of 60 kg). Using a safety factor of 10, the maximum recommended starting dose in humans is approximately 50 mg/kg or a 3,000 mg fixed dose. Based on the proposed 500 mg human dose, the margins based on the HED, C_{max}, and AUC (conservative AUC margin based on partial AUC_{0-t} from TX-7831-0102 and expected AUC_{inf} in humans) are 60-, 87-, and 13.6-fold, respectively, supporting the proposed clinical dose of 500 mg.

4.3.2. Placebo

There is no established treatment for non-hospitalized patients with mild to moderate COVID-19, hence a placebo control is required to distinguish the safety and tolerability

of VIR-7831 from the background signs and symptoms of severe or critical COVID-19 and to evaluate its potential benefit on clinical outcomes

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study through to Week 24. 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:

5.1.1. Age and Risk Factors

1. Participant must be aged 18 years or older AND at high risk of progression of COVID-19 based on presence of one or more of the following risk factors: diabetes (requiring medication), obesity (BMI>35), chronic kidney disease (i.e., eGFR <60 by MDRD), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion), and moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

OR

2. Participant ≥ 55 years old, irrespective of co-morbidities.
    a. Note: target enrollment of ~15% of participants >70 years old

5.1.2. Type of Participant and Disease Characteristics

3. Participants who have a positive SARS-CoV-2 test result (by any validated diagnostic test e.g. RT-PCR, antigen based testing on any specimen type)
   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
   Less than or equal to 5 days from onset of symptoms

5.1.3. Sex and Contraceptive/Barrier Requirements

4. No gender restrictions
5. 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 24 weeks after the last dose of study intervention. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

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

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

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

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

5.1.4. Informed Consent

6. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
   OR
   If participants are not capable of giving written informed consent, alternative consent procedures will be followed as described in Section 10.1.3.

5.2. Exclusion Criteria

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

5.2.1. Medical Conditions

7. Currently hospitalized or judged by the investigator as likely to require hospitalization in the next 24 hours
8. Symptoms consistent with severe COVID-19 as defined by shortness of breath at rest or respiratory distress or requiring supplemental oxygen.
9. Participants who, in the judgement of the investigator are likely to die in the next 7 days.
10. Severely immunocompromised participants, including but not limited to cancer patients actively receiving immunosuppressive chemotherapy or immunotherapy, those with a solid organ transplant or allogeneic stem cell transplant within the last 3 months, or those having conditions requiring the use of systemic corticosteroids equivalent to ≥ 0.5 mg/kg of body weight per day of prednisone within 6 weeks of randomization

11. Known hypersensitivity to any constituent present in the investigational product
12. Previous anaphylaxis or hypersensitivity to a monoclonal antibody

5.2.2. Prior/Concurrent Clinical Study Experience

13. 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.
14. Enrollment in any trial of an investigational vaccine for SARS-CoV-2 .

5.2.3. Other Exclusions

15. Receipt of any vaccine within 48 hours prior to enrollment. Receipt of a SARs-CoV-2 vaccine prior to randomization at any timepoint. Vaccination (including vaccination for SARS-CoV-2) will not be allowed for 4 weeks after dosing.
16. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.
17. Participants who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol through Day 29

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 serious adverse events (SAEs).

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

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

Table 3: Overview of Study Intervention

Arm Name	**VIR-7831**	**Placebo**
Intervention Name	VIR-7831	Placebo to VIR-7831
Type	Biologic	Placebo to Biologic
Dose Formulation	Solution in single-use vial (25 mg/mL)	Sterile 0.9% (w/v) sodium chloride solution
Unit Dose Strength(s)	250 mg/vial (250 mg/10 mL)	Not applicable
Dosage Level(s)	500 mg once	Once
Route of Administration	IV infusion	IV infusion
IMP and NIMP	IMP	IMP
Sourcing	VIR-7831 will be provided centrally by the Sponsor.	Saline for placebo will be provided centrally by Sponsor.
Dosing instructions	Approximately 1-hour infusion time will be used to administer the total dose volume.	Approximately 1-hour infusion time will be used to administer the total dose volume.
Packaging and Labelling	Study intervention will be provided in a single-use vial in an individual carton and labelled as required per country requirement.	Saline will be provided in a single-use vial and labelled as required per country requirement
Current/Former Name(s) or Alias(es)	VIR-7831, GSK4182136	Not applicable

6.2. Preparation/Handling/Storage/Accountability

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

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the pharmacy manual.

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.

Participants will be randomized in a 1:1 ratio to receive study intervention. 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.

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.

6.4. Study Intervention Compliance

Participants will receive VIR-7831 or placebo directly from the investigator or designee, under medical supervision. The date and start and stop times of the dose administered will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

This is a single dose study and 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 treatment physician may provide supportive measures depending on the symptoms.

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

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6.8. Concomitant Therapy

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

- 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.

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

Receipt of any vaccine is not permitted within 4 weeks after dosing. Receipt of any investigational or approved SARS-CoV-2 vaccine is permitted following Week 4. Patients 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.

6.8.2. Permitted Concomitant Medication

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

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

7.1.1. Temporary Discontinuation

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

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the

assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment.

- Study procedures and their timing are summarized in Section 1.3 (Schedule of Activities).
- Select follow-up visits as noted in the Schedule of Activities are planned to be phone call from site to participants. Follow-up visits that include only blood collections may be performed at the clinic or as a home visit.
- 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 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. Screening Period

Informed consent must be obtained before conducting any study procedures. Participant's informed consent will be obtained via a validated and secure e-consent system where available. Screening will be performed no more than 24 hours prior to randomization and include the assessments outlined in the Schedule of Activities (Section 1.3).

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

8.1.1. Medical History

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

8.1.2. SARS-CoV-2 Diagnostic Testing

Documentation of laboratory-confirmed SARS-CoV-2 infection via a validated diagnostic test (e.g. RT-PCR or antigen based testing) 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 ≤ 5 days.

8.1.3. Secondary Contact Information

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

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

8.2. Efficacy Assessments

8.2.1. Hospitalization and Death Data Collection

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

1. Serious Adverse Event (SAE) form
2. Dates that the participant is hospitalized and discharged

3. Dates that the participant is admitted to an intensive care unit
4. Ventilatory support that the participant received
5. Date, time, and cause of death

8.2.2. Active Monitoring of COVID-19 Progression Phone Call

8.2.2.1. Lead-In Phase

During the Lead-In phase of the study, participants will be admitted to a study unit and monitored closely for 7 days after dosing for adverse events, changes in laboratory parameters and progression (or improvement) in disease signs and symptoms. If they do not show signs and symptoms of progression after 7 days, they will be discharged from the study unit.

During Week 2, the participants will be called by the study site daily (except on in-clinic visit days) to monitor 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 site will direct the participant to seek medical attention. In addition, any healthcare encounters or new concomitant medications will be recorded.

8.2.2.2. Expansion Phase

During the Expansion portion of the study, the participants will be called by the study site daily (except on in-clinic visit days) for 14 days post-infusion to monitor 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 site will direct the participant to seek medical attention. In addition, any healthcare encounters or new concomitant medications will be recorded.

8.2.3. Phone Call for Subsequent COVID-19 Illness

In order to monitor participants for subsequent COVID-19 illness after Day 29, participants will be called every 4 weeks through Week 20. This phone call will assess whether the participant was diagnosed again with COVID-19 and whether this illness resulted in any healthcare encounters. Any medications given as a result of this illness will also be recorded.

8.2.4. Participant Reported Outcome Assessments

All questionnaires are planned to be administered using an electronic device where available. Details of the participant reported outcome assessment analyses will be provided in the analysis plan.

8.2.4.1. FLU-PRO Plus Questionnaire

In both the lead-in and expansion phases, participants will complete self-reported presence and severity of COVID-19 symptoms using a COVID-19 adapted FLU-PRO Plus questionnaire.

The questionnaire will be completed where available, once daily with a 24-hour recall, from Day 1 through Day 21, Day 29, Week 8 and Week 12 as outlined in the Schedule of Activities (Section 1.3).

8.2.4.2. Health-related Quality of Life (SF-12 Hybrid)

In the expansion phase, the SF-12 hybrid questionnaire will be used to measure self-reported functional health and well-being where available. Participants will complete the questionnaire with a 24-hour recall on Day 1, Day 15, and Day 29. Starting on Week 8, participants will complete the questionnaire monthly through Week 24 as outlined in the Schedule of Activities (Section 1.3).

8.2.4.3. Work Productivity and Activity Impairment (WPAI)

The WPAI is a validated, patient-reported, quantitative assessment of absenteeism (work time missed), presenteeism (reduced on-the-job effectiveness), work productivity loss and activity impairment due to a specific health problem. In the expansion phase, where available participants will complete the 6-item questionnaire via an electronic device on Day 1, Day 15 and Day 29. Starting on Week 8, participants will complete the questionnaire monthly as outlined in the Schedule of Activities (Section 1.3).

To assess the impact of local shelter-in-place and/or lockdown policies, questions related to social distancing, ability to work on-site / remotely will be asked prior to the WPAI questionnaire.

8.2.5. Long COVID Assessment

To monitor for subsequent development of long COVID during the EOS visit, participants will be asked a series of questions to evaluate a range of symptoms after first being infected with the SARS-CoV-2. These questions will assess whether the participant experienced persistent symptoms since the COVID-19 diagnosis, type of symptoms, frequency, change over time, and impact on social functioning. The questions can be asked and completed via phone call or during the in-clinic visit (see Section 10.6).

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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8.3.2. Vital Signs

Lead-In Phase

During dose administration, vital signs will be monitored every 15 minutes over the 1-hour IV infusion. Vital signs will also be monitored at 1, 2 and 6 hours after infusion. After the first 6 hours after infusion, vital signs will be monitored every 8 hours while the participant is in-clinic.

Expansion Phase

During dose administration, vital signs will be monitored every 15 minutes over the 1-hour IV infusion. Vital signs will also be monitored at 1 hour and 2 hours after infusion.

- Vital sign measurements will include blood pressure, pulse rate, temperature (oral preferred), respiratory rate, and oxygen saturation.
- Blood pressure and pulse measurements will be assessed while participant is semi-supine or sitting with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.3.3. Electrocardiograms

Electrocardiogram will be performed locally. Recording should be reviewed on-site by the investigator.

- For the lead-in phase, 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- For the expansion phase, 12-lead ECG will be obtained prior to dose administration on Day 1.

8.3.4. Cardiac Monitoring

Given the potential for direct myocardial involvement by SARS-CoV-2, it is possible that ADE of disease could manifest as cardiac toxicity (Huang 2020). To monitor this, for participants who develop new or worsening cardiac symptoms, signs or ECG findings suggestive of an acute MI 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.

8.3.5. Virologic Measures

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

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

- Nasopharyngeal swab on Day 1 will include respiratory viral panel to asses coinfection
- Blood samples will be collected for quantitative SARS-CoV-2 RT-PCR

Samples may also be used for resistance surveillance analysis.

8.3.6. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.
- Laboratory assessments at Screening visit for the Lead-In phase and Expansion phase will be performed locally at the clinical site.
- To ensure timely safety management of the participants, local laboratory assessments per standard of care at the clinical site will be performed for the in-patient portion of the Lead-In phase as outlined in the Schedule of Activities.
- In the Lead-In phase only, urine will be collected on Day 1 (pre-dose) and Day 2 for analysis of albumin to creatinine ratio conducted locally.
- All protocol-required laboratory test performed centrally, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and Schedule of Activities (Section 1.3)
  - The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
  - Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
  - All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.7. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at Screening to confirm eligibility and at Week 24 or Early Withdrawal visit.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

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

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

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

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

Since hospitalization or death are SAEs and they are included in the primary endpoint, they will be collected and reported as SAEs as delineated in Section 8.4.1 below. Since it will not be possible to delineate in a single participant whether the hospitalization is directly related to COVID-19 complications or could be related to VIR-7831 causing more severe disease due to ADE, all hospitalizations regardless of cause will be included in the primary endpoint and will also be counted as serious adverse events (with the exception of elective treatment of a pre-existing condition that did not worsen from baseline as noted in Section 10.3).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7). As noted in Section 8.2.1 data on hospitalization or death should additionally be recorded in the eCRF for all relevant sections.

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

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

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

8.4.2. Assessment of Severity

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

8.4.3. Method of Detecting AEs and SAEs

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

8.4.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.8), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.4.5. Regulatory Reporting Requirements for SAEs

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.

8.4.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until Week 24.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to sponsor or designee within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy and for up to 1 year after birth. The investigator will collect follow-up information on the participant and the neonate/child and the information will be forwarded to the sponsor or designee.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor or designee as described in Section 8.4.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.7. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3 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 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.

8.4.8. 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
- Immunogenicity related adverse drug reactions
- Adverse events potentially related to antibody dependent enhancement of disease

8.4.8.1. Infusion-Related Reactions and Serious Hypersensitivity

Pleae refer to local or institutional guidelines for monitoring relevant adverse events encompassing hypersensitivity, angioedema, anaphylaxis, acute anaphylactic shock and minor allergic episodes. Pre-medications will be permitted at the investigator's discretion and will be appropriately documented.

8.4.8.2. Immunogenicity

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

8.4.8.3. Antibody Dependent Enhancement

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

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

The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations (Arvin 2020). This study will include participant follow-up for a period of 5 half-lives to assess for the potential of enhanced disease in the context of waning 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 temporally associated with VIR-7831 infusion or as increased severity or duration of illness in VIR-7831-treated participants vs. placebo-treated participants.

As described in Section 2.3.1, AEs potentially related to ADE of the disease will be reviewed by the IDMC to see if there is an imbalance in incidence or severity between the treatment groups.

8.5. Pharmacokinetics

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

- The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of VIR-7831 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- At visits during which whole blood samples are collected to obtain serum endpoints other than PK 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.

For the intensive sub-study in the Lead-In phase, pharmacokinetic parameters will be computed using standard noncompartmental methods. Parameters may include, but not be limited to C_{max}, C_{last}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, $\%AUC_{exp}$, $t_{1/2}$, λ_z, V_z, V_{ss}, CL, and will be listed and summarized using descriptive statistics. Other parameters may be calculated, if deemed necessary. Definitions of PK parameters and methods for estimation will be included in the analysis plan.

For the Expansion Phase, serum concentrations may be combined with data from the Lead-In Phase in addition to other studies evaluating VIR-7831 for the purpose of population PK model development. Pharmacokinetic analyses may be conducted to explore exposure-response relationships between PK parameters and selected antiviral variables. These analyses may include graphical plots, tabular summaries, and various linear and/or nonlinear analyses. Details of the PK analyses will be provided in the analysis plan.

8.6. Genetics

A 2.5 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Sequencing of four genomic polymorphisms in FCGR2A, FCGR2B, FCGR3A, and IGHG1 loci will be performed on whole blood samples collected pre-dosing in all participants. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

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

8.7. Biomarkers

Multiple immunology/biomarker samples will be collected from participants to evaluate host immune responses and exploratory biomarkers related to SARS-CoV-2 and/or VIR-7831, including genetic, cellular, transcriptomic, virologic, and proteomic parameters.

Whole blood samples will be collected for RNAseq to evaluate cellular populations and transcriptomes at early timepoints after treatment. This is an optional test requiring consent from patients. Serum will be collected throughout the course of the study to evaluate changes in serum biomarkers and cytokines at early timepoints following treatment (including but not limited to inflammatory cytokines and chemokines, such as IL-6, IFN-alpha, IL-1, IL-3, TNF-alpha, as available), as well as to evaluate the host antibody response to SARS-CoV-2 antigens over the duration of the study. In a sub-study, PBMCs will be collected to assess the frequency and function of SARS-CoV-2 specific T cells.

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

Sponsor may store samples for up to 15 years after the end of the study to achieve study objectives.

8.7.1. Resistance Analyses

In order to monitor for resistance, resistance surveillance will be conducted for all participants who are randomized and dosed. Deep sequence analysis of the SARS-CoV-2 spike gene will be attempted on baseline and post-baseline (from participants who do not experience a decline in viral load or who experience virologic rebound) nasopharyngeal samples to identify substitutions in the mAb epitope or substitutions outside the epitope that arise during treatment. Virologic rebound will be defined as participants who experience an increase of >1 $\log_{10}$ copies/mL in viral load for 2 consecutive visits, or viral load becomes quantifiable for 2 consecutive visits after having been below the limit of quantification. For identified substitutions that qualify for phenotypic analysis, in vitro phenotypic analysis of the antiviral activity of VIR-7831 using a SARS-CoV-2 spike pseudovirus system will be attempted and analysed for reduced susceptibility to VIR-7831.

8.8. 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).

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of this study is to evaluate the efficacy or VIR-7831 versus placebo in preventing the progression of COVID-19.

The primary endpoint is proportion of participants who have progression of COVID-19 through Day 29 as defined by hospitalization > 24 hours for acute management of illness or death.

If we denote the proportion of participants with progression of COVID-19 in the VIR-7831 arm as P_A, and the proportion of participants with progression of COVID-19 in the placebo arm as P_B, the following null and alternative hypothesis for superiority is as follows:

H0: $P_A = P_B$

H1: $P_A \neq P_B$

9.2. Sample Size Determination

VIR-7831 and placebo will be randomized in a 1:1 ratio.

The study will utilize a group sequential design with two interim analyses to asses both futility due to lack of efficacy and overwhelming efficacy. A Lan-DeMets alpha-spending function to control the type I error will be used, using a Pocock analogue rule for futility and a Hwang-Shih-DeCani (with parameter $\gamma = 1$) analogue for efficacy [Hwang 1990].

The expected sample size is 680 participants per arm No sample size re-estimation is planned.

Approximately 1360 (680 per arm) participants will be randomly assigned to study intervention. A total sample size of 1360 will provide approximately 90% power to detect a 37.5% relative efficacy in reducing progression of COVID-19 through Day 29 at the overall two-sided 5% significance level with assumed progression of COVID-19 rates of 16% in the placebo arm and 10% in the VIR-7831 arm, respectively. The minimal detectable efficacy for this design at the final efficacy analysis is approximately 25% if disease progression rates is 16% in the placebo arm.

9.3. Analysis Sets

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

Participant Analysis Set	Description
Intent-to-Treat	All participants who were randomized according to the intervention they were randomized to. This will be the primary analysis set.
Safety	All randomized participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
Per-Protocol	All participants in the ITT analysis set for whom there were no major protocol deviations that impact the primary analyses. Data should be reported according to the intervention a participate was randomized to. Specific details of major protocol deviations that would exclude participants from the PP analysis will be defined in the analysis plan
Pharmacokinetic	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)
Virology	All participants who were randomized according to the intervention they were randomized to and with a central lab confirmed quantitative nasopharyngeal swab at Day 1. This will be the primary analysis set for virology.

Defined Analysis Data Sets	Description
Analysis set for all efficacy estimands	All randomized participants. For participants who discontinue study intervention and/or receive rescue therapy, all post discontinuation or post rescue observations will be included in the analysis set.
Analysis set for all safety estimands	All randomized participants. For participants who discontinue study intervention and/or receive rescue therapy, all post discontinuation or post rescue observations will be included in the analysis set.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to unblinding for the first IDMC and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the

change will be described in the statistical analysis plan. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.1. General Considerations

In the case of a difference between the stratification assigned at the time of randomization and the data collected in the eCRF, the analyses will be performed based on the calculated stratum at randomization.

Confidence intervals will use the 95% levels unless otherwise specified.

9.4.2. Primary Endpoint(s)

The primary endpoint will be proportion of participants who have progression of COVID-19 as defined by hospitalization > 24 hours for acute management of illness or death through Day 29.

The primary analysis will be the comparison of progression rate within 29 days between VIR-7831 and placebo using generalized linear model (GLM) with log binomial link, adjusted for treatment (VIR-7831 vs. placebo), duration of symptoms (≤3 days vs. 4-5 days) , age (≤70 vs. >70 years old) and gender (female vs. male) to test for superiority of VIR-7831 versus placebo. If the GLM does not converge then it will be approximated by a Poisson regression model with a robust sandwich estimator, adjusted for the same covariates of GLM. If the P-value from the GLM (or from Poisson regression model if GLM does not converge) is less than the adjusted significance level02446, a statistically significant advantage in favor of VIR-7831 will be declared. Relative risk of VIR-7831 versus placebo and its 95% confidence interval (CI) will be estimated. At each of the interim and final efficacy analysis, appropriate CI based on the adjusted significance level will also be provided.

Possible intercurrent events are withdrawal of consent and lost-to-follow-up on or before Day 29. The strategy for analysis for these intercurrent events, will be to use the treatment policy strategy, with data analyzed as collected. It is expected missing data will be minimal and most will be lost to follow up data after discharge and this along with intermittent data will be imputed using multiple imputation under the missing at random assumption. Every effort will be made to reduce missing data (refer to Section 7) . Supplemental estimand strategies and missing data sensitivities will be performed and further details will be provided in the analysis plan.

9.4.3. Secondary Endpoint(s)

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

9.4.4. Exploratory Endpoint(s)

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

9.4.5. Safety Analysis

For safety data, no formal hypotheses will be tested. Occurrence of AEs, non-COVID-19-related AEs, SAEs, non-COVID 19 relate SAEs, and AESIs, including laboratory tests, vital signs, and ECG abnormalities will be displayed in the form of listings, frequencies, summary statistics, graphs, and statistical analyses where appropriate. Interpretation will be aided by clinical expertise.

As noted in Section 8.4, 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 included in the primary endpoint and will also be counted as serious adverse events. To inform on the number and nature of non-COVID-19 adverse events and serious adverse events, additional safety analyses will be performed in which select, pre-specified terms consistent with known progression of COVID-19 disease will be excluded. Details of these and all analyses, including example outputs, will be documented in the analysis plan.

9.4.6. Other Analysis

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

9.5. Interim Analysis

Interim analysis will be used to assess safety (due to harm), futility due to lack of efficacy and efficacy. A non-binding statistical framework for evaluating number of events of interest will be provided to aide the IDMC to make recommendations based upon the totality of available safety data from the study.

Full details of timing of analyses and all stopping criteria will be given in the IDMC charter.

Interim analyses to assess efficacy and futility are planned when approximately 41% and 64% of the required number of participants have reached Day 29 visit. The analysis of the primary endpoint at the interim analyses will be the same as that described for the primary endpoint. Group sequential techniques will be used to adjust stopping boundaries to reflect the actual number of participants with available data for primary endpoint at the time of each interim analysis. The full decision criteria for the futility due to lack of efficacy and efficacy rules along with additional information to be presented to the IDMC will be defined in the IDMC charter and associated documents, as well as the analysis plan.

The Joint Safety Review Team (JSRT) comprising individuals from Vir and GSK will review blinded safety data at regular intervals throughout the conduct of the study and determine if a safety concern based on instream blinded data review needs to be escalated to the IDMC. Details of the JSRT process is recorded in relevant SRT documents.

Following all participants completing the final follow-up visit at Week 24, a final safety analysis will be performed.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

Vir (alone or working with others) may use the participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about 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.

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10.1.5. Committees Structure

Independent Data Monitoring Committee (IDMC)

An IDMC will actively monitor interim unblinded safety (Lead-In Phase) and interim unblinded safety and efficacy data (Expansion Phase) to make recommendations to Vir as detailed in the IDMC Charter. The IDMC members will include at least 2 physicians with relevant medical training and one statistician. Details regarding the IDMC process will be available in relevant IDMC documents.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews are outlined in the IDMC Charter, which is available upon request.

Joint Safety Review Team

The Joint Safety Review Team (JSRT) comprised of individuals from Vir and GSK will review blinded safety data at regular intervals throughout the conduct of the study and determine if a safety concern based on instream blinded data review needs to be escalated to the IDMC. Details of the JSRT process is recorded 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.
- As hospitalization and mortality are both primary study endpoints and serious adverse events, instream data cleaning including updating and reconciliation of hospitalization events between the safety dataset and efficacy dataset will be performed throughout the study duration and any changes or updates to the SAEs of hospitalization or mortality will be reflected in the efficacy dataset.

10.1.8. Source Documents

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

10.1.10. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 4 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 4: Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
	Hematocrit	ABO typing[2]	Urine albumin to creatinine ratio[3]	
Hematology	Platelet Count	RBC Indices:	WBC count with Differential:	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
		%Reticulocytes	Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine[6]	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)			
Inflammatory Markers[1]	C-reactive protein[1, 5]	Ferritin[1, 5]	IL-6[1, 5]	
Respiratory Pathogens[4]	Respiratory viral panel by PCR[4]			

[1] Parameters not included in local laboratory assessments performed at Screening visit
[2] Screening visit only to be performed locally
[3]Lead-In phase only: Day 1 (pre-dose) and Day 2 to be performed locally.
[4] Day 1 only and performed by central laboratory
[5] Day 1, 15 and 29 visits only and performed by central laboratory
[6] Repeat if above the 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
a. 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
b. An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. c. 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. d. 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. e. Solicited AEs are predefined local at the infusion site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events <u>Meeting</u> 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.

Events Meeting the AE Definition
• Clinically significant changes in laboratory assessments.

Events NOT Meeting the AE Definition
1. 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. 2. 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. 3. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. 4. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). 5. 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:	
1) Results in death	
2) 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.	
3) Requires inpatient hospitalization or prolongation of existing hospitalization	
Appendix A.	In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Appendix B.	Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4) Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.	

An SAE is defined as any serious adverse event that, at any dose:
• 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.
5) Is a congenital anomaly/birth defect
6) 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: a. Myocardial infarction/unstable angina b. Congestive heart failure c. Arrhythmias d. Valvulopathy e. Pulmonary hypertension f. Cerebrovascular events/stroke and transient ischemic attack g. Peripheral arterial thromboembolism h. Deep venous thrombosis/pulmonary embolism i. Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
a. 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. b. The investigator will then record all relevant AE/SAE information.

AE and SAE Recording
c. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the required form. d. There may be instances when copies of medical records for certain cases are requested by GSK Pharma Safety staff. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission. e. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

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 sponsor 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.

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.

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

Expedited Reporting
The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events to identify and expeditiously communicate new safety findings to investigators, IRBs, ECs, and health authorities based on applicable legislation. To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the VIR-7831 Investigator's Brochure.

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
  • oral
  • 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: Genetics

10.5.1. USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to VIR-7831 mechanism of action in SARS-CoV-2 and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to VIR-7831 and related mAb therapeutics for SARS-CoV-2 and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analyzed for genomic polymorphisms in FCGR2A, FCGR2B, FCGR3A, and IGHG1 loci.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to VIR-7831 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on VIR-7831 (or study interventions of this class) or SARS-CoV-2 continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Long COVID Questionnaire

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.

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