Statistical Analysis Plan

Study ID: 216912

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

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TITLE PAGE

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

Protocol Number: VIR-7831-5006 (GSK 4182136 Study 216912)

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

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

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

Sponsor Name:

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

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1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for VIR-7831/GSK4182136 Study 5006/216912.

This document will include the planned analyses in each of Parts A, B and C based on most recent Protocol Amendment 05 (Dated: 29-10-2021).

Data from each part of the study will be reported separately in respective study reports and not combined.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
Safety (Part A) To evaluate the safety and tolerability profile of intravenous (IV) VIR-7831 Gen2 and IV Gen1	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29 • Occurrence of adverse events of special interest (AESIs) through Day 29 • Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29 • Occurrence of disease progression events (not classified as AEs) through Day 29
Pharmacodynamics (Part B) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via intramuscular (IM) injection (500 mg) in the upper respiratory tract	• Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUCD1-8) in nasopharyngeal swab samples
Pharmacodynamics (Part C) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg)	• Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to

Objectives	Endpoints
and via IM injection (250 mg) in the upper respiratory tract	Day 8 (AUCD1-8) in nasopharyngeal swab samples
Secondary	
Safety (Part A) To evaluate the safety and tolerability profile of IV VIR-7831 Gen2 and IV Gen1	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 24 • Occurrence of AESIs through Week 24 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 24
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, through Day 29	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29 • Occurrence of adverse events of special interest (AESIs) through Day 29 • Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29 • Occurrence of disease progression events (not classified as AEs) through Day 29
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, through End of Study (EOS)	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 36 • Occurrence of AESIs through Week 36 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 36

Objectives	Endpoints
Virology (Part A) To characterize the effect of VIR-7831 Gen2 IV and Gen1 IV on the viral shedding profile in the upper respiratory tract	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from saliva and nasal mid-turbinate swabs samples
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and Gen2 IM on the viral shedding profile in the upper respiratory tract	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from nasopharyngeal (NP) swab samples • Proportion of participants with undetectable viral load at all visits through Day 29 of the study as measured by qRT-PCR from NP swab samples • Mean area under the curve of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 5 (AUCD1-5) and Day 1 to 11 (AUCD1-11)
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and IM on viral load clearance in the upper respiratory tract	• Proportion of individuals with a persistently high viral load at Day 8 as assessed via qRT-PCR in NP swab samples (see Part B and C of Section 4.3.1.2)
Pharmacokinetics (Part A, Part B, and Part C) To assess the pharmacokinetics (PK) of VIR-7831 Gen2 IV and IM and Gen1 IV in serum	• Serum PK of VIR-7831
Pharmacokinetics (Part B and C) To assess the absolute bioavailability of VIR-7831 Gen2 IM relative to Gen2 IV	• Area under the plasma concentration-time curve, AUC_{inf}
Pharmacokinetics (Part B and C) To assess whether the systemic exposure of VIR-7831 Gen2 IM increases proportionately with dose	• Dose-proportionality assessment using dose normalized AUC_{inf}, AUC_{last}, AUC_{D1-D29}, and C_{max}

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

1.1.2. Estimands

Each study objective is presented below with additional information, including prespecified estimands with related attributes.

- **Treatment condition:**

  Part A: VIR-7831 (sotrovimab) Gen 1 500 mg IV versus VIR-7831 (sotrovimab) Gen 2 500 mg IV

  Part B: VIR-7831 (sotrovimab) Gen 2 500 mg IM versus VIR-7831 (sotrovimab) Gen 2 500 mg IV

  Part C: VIR-7831 (sotrovimab) Gen 2 250 mg IM versus VIR-7831 (sotrovimab) Gen 2 500 mg IV

- **Population:** Non-hospitalized patients with mild to moderate COVID-19, aged >=18 years and < 70 years (for Parts B and C).

Table 1 Estimands

Objective	**Estimand Category**	**Estimand** **Variable(s)/ Endpoint(s)**	**Analysis Set**	**Intercurrent Events & Strategy**	**Population Level Summary Measure**
Safety (Part A) To evaluate the safety and tolerability profile of intravenous (IV) VIR-7831 Gen2 and IV Gen1	Primary	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29 • Occurrence of adverse events of special interest (AESIs) through Day 29	Safety Set	**Intercurrent Events**: Death (if not part of the endpoint definition, for e.g., in AE and SAE), COVID-19 Vaccination and use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Frequency and Percentages

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
		• Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29 • Occurrence of disease progression events (not classified as AEs) through Day 29			
Pharmacodynamics (Part B) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via intramuscular (IM) injection (500 mg) in the upper respiratory tract	Primary	• Mean area under the curve from Day 1 to Day 8 (AUC_{D1-8}) of SARS-CoV-2 viral load as measured by qRT-PCR in NP swab samples	Viral Pharmacodynamic Set	**Intercurrent events:** Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy for Death**: Composite strategy, where subjects who die prior to Day 8, their AUC(D1-8) viral load value will be imputed using the worst AUC viral load value from other subjects in the same treatment arm. The strategy for all the other intercurrent events (as applicable for this endpoint) will	Ratio of mean log_{10} AUC

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
				be treatment policy where data will be reported as captured.	
Pharmacodynamics (Part C) To evaluate the virological response of VIR-7831 Gen2 administered IV (500 mg) and via IM injection (250 mg) in the upper respiratory tract	Primary	• Mean area under the curve from Day 1 to Day 8 (AUC_{D1-8}) of SARS-CoV-2 viral load as measured by qRT-PCR in NP swab samples	Viral Pharmacodynamic Set	**Intercurrent events:** Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy for Death**: Composite strategy, where subjects who die prior to Day 8, their AUC(D1-8) viral load value will be imputed using the worst AUC viral load value from other subjects in the same treatment arm. The strategy for all the other intercurrent events (as applicable for this endpoint) will be treatment policy where data will be reported as captured.	Ratio of mean log_{10} AUC
Safety (Part A) To evaluate the safety and tolerability profile of IV VIR-7831 Gen2 and IV Gen1	Secondary 1	• Occurrence of non-serious AEs through Week 12	Safety Set	**Intercurrent Events**: Death (if not part of the endpoint definition, for e.g., in AE and SAE), COVID-19 Vaccination and use of other COVID-19 therapies.	Frequency and Percentages

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
		• Occurrence of SAEs through Week 24 • Occurrence of AESIs through Week 24 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 24		**Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, through Day 29	Secondary 1	• Occurrence of adverse events (AEs) through Day 29 • Occurrence of serious adverse events (SAEs) through Day 29 • Occurrence of adverse events of special interest (AESIs) through Day 29	Safety Set	**Intercurrent Events**: Death (if not part of the endpoint definition, for e.g., in AE and SAE), COVID-19 Vaccination and use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events	Frequency and Percentages

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
		• Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29 • Occurrence of disease progression events (not classified as AEs) through Day 29		where data will be reported as captured.	
Safety (Part B and C) To evaluate the safety and tolerability profile of VIR-7831 Gen2 administered via IV infusion and IM injection, through End of Study (EOS)	Secondary 2	• Occurrence of non-serious AEs through Week 12 • Occurrence of SAEs through Week 36 • Occurrence of AESIs through Week 36 • Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12 • Occurrence of disease progression events (not classified as AEs) through Week 36	Safety Set	**Intercurrent Events**: Death (if not part of the endpoint definition, for e.g., in AE and SAE), COVID-19 Vaccination and use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Frequency and Percentages

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
Virology (Part A) To characterize the effect of VIR-7831 Gen2 IV and Gen1 IV on the viral shedding profile in the upper respiratory tract	Secondary 2 (Part A)	• Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from saliva and nasal mid-turbinate swabs samples	Virology Set	**Intercurrent events:** Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Difference of mean change from baseline
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and Gen2 IM on the viral shedding profile in the upper respiratory tract	Secondary 3	• Change from baseline in log_{10} viral load at all visits till Day 29 as measured by qRT-PCR from NP swab samples	Viral Pharmacodynamic Set	**Intercurrent events:** Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Difference of mean change from baseline
	Secondary 3	• Proportion of participants with undetectable viral load at all visits till Day 29 of the study as measured by qRT-	Viral Pharmacodynamic Set	Intercurrent event: Death, COVID-19 Vaccination and Use of other COVID-19 therapies. Strategy for Death: Composite strategy where participants	Frequency and Percentages by visits

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
		PCR from NP swab samples		who die before Day 29 will be considered to have not met the undetectable viral load status at all visit post the intercurrent event of death. The strategy for all the other intercurrent events (as applicable for this endpoint) will be treatment policy where data will be reported as captured.	
	Secondary 3	• SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 5 (AUC_{D1-5}) and Day 1 to 11 (AUC_{D1-11})	Viral Pharmacodynamic Set	**Intercurrent events:** Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy for Death**: Composite strategy, where subjects who die prior to Day 5 or 11, their AUC viral load value will be imputed using the worst AUC viral load value from other subjects in the same treatment arm. The strategy for all the other intercurrent events (as	Ratio of mean log_{10} AUC

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
				applicable for this endpoint) will be treatment policy where data will be reported as captured.	
Virology (Part B and C) To characterize the effect of VIR-7831 Gen2 IV and IM on viral load clearance in the upper respiratory tract	Secondary 4	• Proportion of individuals with a persistently high viral load at Day 8 as assessed via qRT-PCR in NP swab samples	Viral Pharmacodynamic Set	**Intercurrent event:** Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy for Death**: Composite strategy where participants who die prior to Day 8 will be considered to have met the persistently high viral load criteria at Day 8. The strategy for all the other intercurrent events (as applicable for this endpoint) will be treatment policy where data will be reported as captured.	Frequency and Percentage
Pharmacokinetics (Part A, Part B, and Part C)	Secondary 3 (Part A)/ Secondary 5 (Part B and Part C)	• Serum PK concentration and parameters of VIR-7831	PK Set	**Intercurrent Events**: Death, COVID-19 Vaccination and use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all	Log transformed Parameters will be presented with - Geometric mean, 95% confidence interval for the

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
To assess the pharmacokinetics (PK) of VIR-7831 Gen2 IV and IM and Gen1 IV in serum				possible intercurrent events where data will be reported as captured.	geometric mean (optional), Standard deviation of the log-transformed data (SD logs), Between subject coefficient of variation (%CVb) Untransformed parameters will be presented with - Arithmetic mean, 95% confidence interval for the arithmetic mean (optional), Standard deviation of the untransformed data (SD), Median, Min, Max, %CV

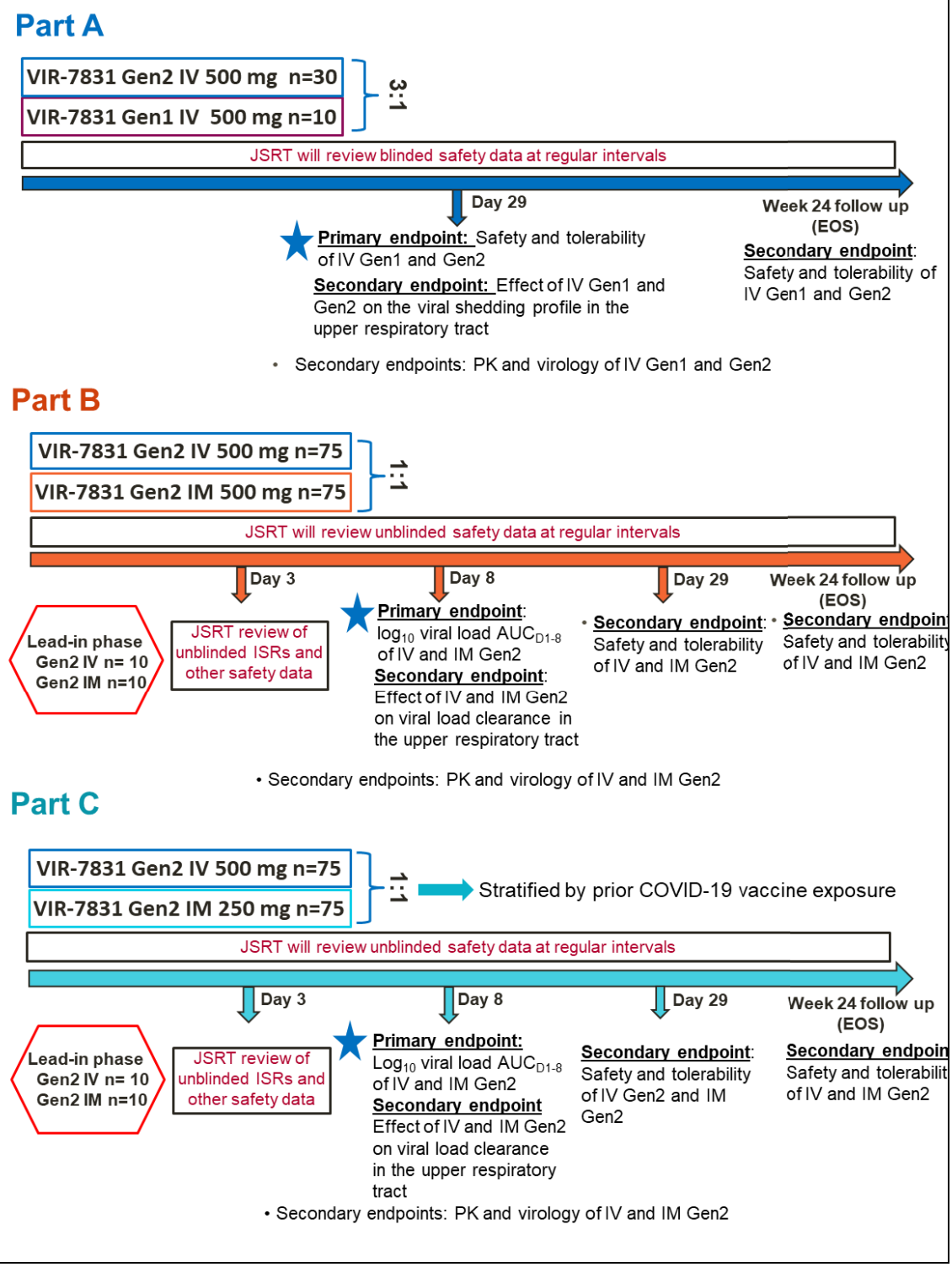
Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
Pharmacokinetics (Part B and C) To assess the absolute bioavailability of VIR-7831 Gen2 IM relative to Gen2 IV	Secondary 6	• Area under the plasma concentration time curve, AUC_{inf}	PK Set	**Intercurrent Events**: Death, COVID-19 Vaccination and use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Ratio of mean log_e AUC_{inf}
Pharmacokinetics (Part B and C) To assess whether the systemic exposure of VIR-7831 Gen2 IM increases proportionately with dose	Secondary 7	• Dose-proportionality assessment using dose normalized AUC_{inf}, AUC_{last}, AUC_{D1-D29}, and C_{max}	PK Set	**Intercurrent Events**: Death, COVID-19 Vaccination and use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Ratio of mean log_e AUC_{inf}, AUC_{last}, AUC_{D1-D29}, and C_{max}

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
Resistance (Part A, Part B, and Part C) To monitor emergence of SARS-CoV-2 resistant mutants against VIR-7831	Exploratory 1	• Presence at Baseline and emergence of SARS-CoV-2 viral resistance mutants	Safety Set	**Intercurrent event**: Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy**: The strategy for all intercurrent events (as applicable for this endpoint) will be treatment policy where data will be reported as captured.	Frequency counts of subjects with viral resistance (if appropriate) and listing
Immunogenicity (Part A, Part B, and Part BC) To assess the immunogenicity of VIR-7831 Gen2 IV and IM and Gen1 IV	Exploratory 2	• Incidence and titers (if applicable) of serum anti-drug antibodies (ADA) to VIR-7831	Safety Set	**Intercurrent Events**: Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Frequency counts

Objective	Estimand Category	Estimand Variable(s)/ Endpoint(s)	Analysis Set	Intercurrent Events & Strategy	Population Level Summary Measure
Immunology (Part A, B and Part C) To assess the effect of VIR-7831 Gen2 IV and IM and Gen1 IV on immune response	Exploratory 3	Incidence of anti-N, anti-S and anti-RBD SARS CoV-2 antibodies at Baseline to investigate effect of immune status on response.	Safety set	**Intercurrent Events**: Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Frequency counts
		• Incidence of anti-N SARS CoV-2 antibodies at Day 29 to investigate effect of VIR-7831 treatment on development of immunity.	Safety set	**Intercurrent Events**: Death, COVID-19 Vaccination and Use of other COVID-19 therapies. **Strategy**: A Treatment Policy Strategy will be used for all possible intercurrent events where data will be reported as captured.	Frequency counts

1.2. Study Design

Overview of Study Design and Key Features



Overview of Study Design and Key Features	
Design Features	This study is a Multicenter, Randomized, Double-Blind, Parallel Group Phase II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of a Second Generation VIR-7831 Material in Non-Hospitalized Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19). Screening assessments will be performed within 1 day before the start of the IV infusion or IM injections. After completion of screening and baseline assessments, eligible participants will be randomized. Part A will be randomized in a 3:1 ratio to receive a single dose of 500 mg intravenous infusion of either Gen2 or equal volume Gen1 study material. Day 1 monitoring will take approximately 9 hours for safety assessments and intensive PK sampling. Part B and Part C will be randomized in a 1:1 ratio to receive a single dose of VIR-7831 Gen2 IV or Gen2 IM, by IRT on Day 1. Part C will be stratified by prior exposure to an authorized or approved SARS-CoV-2 vaccine. Part B and Part C will be open-label, and participants will only receive the intervention that he/she is randomized to receive (i.e., there is no additional placebo administered IV or IM). In the Lead-in phase of Part B and Part C, approximately 20 participants will be enrolled and randomly assigned (1:1) to receive either Gen2 IV or Gen2 IM. A review of injection site reactions (ISRs), infusion-related reactions (IRRs), and other safety and tolerability data through Day 3 will be performed by the Joint Safety Review Team (JSRT). Enrolment for the Expansion phase for Part B and part C will begin after completion of enrolment of the Lead-in phase of Part B and Part C; however, the change from 2 hours to 1 hour for Part B or 1 hour to 30 minutes for Part C of monitoring post-injection or post-infusion will not occur until a recommendation to reduce monitoring time from the JSRT is received, following review of the Day 3 data from the Lead-in phase. In the Expansion phase, approximately 130 participants will be randomly (1:1) assigned to receive Gen 2 IV or Gen 2 IM. Any participant who receives the study intervention will be considered evaluable. Part B of the study will be open-label and participants will be randomized 1:1 to receive a 500 mg dose of Gen2 material by IV infusion or IM injection. Part C of the study will be open-label and participants will be randomized 1:1 to receive a 500 mg dose of Gen2 material by IV infusion or 250 mg dose of Gen2 material by IM injection.
Study intervention	**Part A:** VIR-7831 Gen1 Solution in single use vial (25mg/mL) or VIR-7831 Gen2 Solution in single use vial (62.5mg/mL) Both IMPs will be administered at dose level 500 mg as an IV injection.

Overview of Study Design and Key Features	
	Part B: VIR-7831 Gen2 Solution in single use vial (62.5mg/mL) Both IMPs will be administered at dose level 500 mg as an IV infusion or IM injection. The IM injection will be performed as two 4 mL injections, one in each dorsogluteal muscle. **Part C:** VIR-7831 Gen2 Solution in single use vial (62.5mg/mL) The IV infusion will be administered at dose level 500 mg whereas IM injection will be administered at dose level 250 mg. The IM injection will be performed as single 4 mL injection in a dorsogluteal muscle or as two 2 mL injections, one in each deltoid muscle.
Study intervention Assignment	**Part A:** After completion of screening and baseline assessments, eligible participants will be randomized in a 3:1 ratio to VIR-7831 Gen2 or Gen1, by interactive response technology (IRT) in a blinded manner and treated with a single IV dose of the study intervention on Day 1. **Part B:** After completion of screening and baseline assessments, eligible participants will be randomized in a 1:1 ratio to receive a single dose of VIR-7831 Gen2 IV (500 mg) or Gen2 IM (500 mg, performed as two 4 mL injections, one in each dorsogluteal muscle.), by IRT on Day 1. Part B will be open-label, and participants will only receive the intervention that he/she is randomized to receive (i.e., there is no additional placebo administered IV or IM). **Part C:** After completion of screening and baseline assessments, eligible participants will be randomized in a 1:1 ratio to receive a single dose of VIR-7831 Gen2 IV (500 mg) or Gen2 IM (250 mg, performed as single 4 mL injection in a dorsogluteal muscle or as two 2 mL injections, one in each deltoid muscle), by IRT on Day 1. Part C will be open-label, and participants will only receive the intervention that they are randomized to receive (i.e., there is no additional placebo administered IV or IM). **Part A, Part B and part C:** All participants will receive SoC as per institutional protocols, in addition to the study intervention.

Overview of Study Design and Key Features	
Interim Analysis	No interim analyses will be conducted in the study. However, once the last participant recruited completes the primary assessment in each Part, the data will be analyzed to allow a readout of the primary and selected secondary endpoints. Participants in Part A of the study will continue to complete the remaining scheduled assessments till the end of study at Week 24. Participants in Part B and C of the study will continue till the end of study at Week 36.

2. STATISTICAL HYPOTHESES

Part A:

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

Part B:

The primary objective of this Part B of the study is to evaluate the viral pharmacodynamics of VIR-7831 Gen2 material administered via IV infusion and IM injection, specifically via assessments of log10 SARS-CoV-2 viral load AUC(D1-8) following a single dose of 500 mg IV or a single dose of 500 mg IM.

The time period of 8 days has been selected to optimize the sensitivity of the AUC signal given the propensity for negative PCR results in the majority of trial participants by Day 28 [Chen, 2021].

Secondary objectives include evaluating the safety, tolerability, and pharmacokinetics of VIR-7831 Gen2 material administered via IM injection.

Part C:

The primary objective of Part C of the study is to evaluate the viral pharmacodynamics of VIR-7831 Gen2 500 mg IV compared to Gen2 250 mg IM, specifically via assessments of log10 SARS-CoV-2 viral load AUC(D1-8) following a single dose of 500 mg IV or a single dose of 250 mg IM.

Similar to Part B, the time period of 8 days has been selected to optimize the sensitivity of the AUC signal given the propensity for negative PCR results in the majority of trial participants by Day 28 [Chen, 2021].

Secondary objectives include evaluating the safety, tolerability, and pharmacokinetics of VIR-7831 Gen2 material administered via IM injection.

3. ANALYSIS SETS

3.1. Part A Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population (Screening Pass and Failures)
Enrolled	All participants who entered the study after successful screening. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomized	All participants who were randomly assigned to study intervention in the study. Participants who were randomised by error are also included in the Randomized Set. Data should be reported according to the randomized intervention.	Study Population
Safety	All randomized participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.	Safety, Exploratory and Study Population
Virology	All participants in the Safety analysis set with a central lab confirmed quantifiable[1] nasal mid-turbinate and/or saliva swab at baseline[2]. Data should be reported according to the intervention they actually received.	Virology
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analyzed according to the intervention they actually received.	PK

[1] Quantifiable viral load is defined as samples which are not <LLOD (or negative) and not <LLOQ (or <2.08).

[2] Baseline viral load is defined as the non-missing assessment taken at Day 1.

3.2. Part B and Part C Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population (Screening Pass and Failures)
Enrolled	All participants who entered the study after successful screening. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomized	All participants who were randomly assigned to study intervention in the study. Participants who were randomised by error are also included in the Randomized Set. Data should be reported according to the randomized intervention.	Study Population
Safety	All randomized participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.	Safety, Exploratory and Study Population
Viral Pharmacodynamic (PD)	All participants in the Safety analysis set who had a baseline[2] (Day 1) quantifiable[1] viral load as assessed using qRT-PCR from NP swabs. Data should be reported according to the intervention they actually received.	PD and other Virology
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analyzed according to the intervention they actually received.	PK

[1] Quantifiable viral load is defined as samples which are not <LLOD (or negative) and not <LLOQ (or <2.08).

[2] Baseline viral load is defined as the non-missing assessment taken at Day 1.

4. STATISTICAL ANALYSES

4.1. General Considerations

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

4.1.1. General Methodology

In general, in Parts A, B and C, the Screened Set will be used to summarize screen failures.

The Enrolled and Randomized Sets will be used for relevant Study Population summaries.

The Safety Set will be used for relevant Study Population summaries (including disposition, demographics, baseline disease characteristics (including baseline virology data), medical history and current medical conditions), as well as for all safety summaries (including Adverse events, Laboratory data, ECG, Vital Signs, Supplemental oxygen, Concomitant medications etc.) and the PK Set will be used for PK summaries.

The signs and symptoms data will be summarized using number and percentages by visit for Part A. For Part B and Part C, signs and symptoms will be presented by visit and grade using the Safety Set.

The proportion of participants with risk factors leading to disease progression will be summarized by the Safety set.

Additional descriptive summaries may be presented in Part B and Part C for healthcare encounters data including hospitalizations, emergency room visits etc.

In Part A, the Virology Set will be used for all Virology endpoint analyses.

In Part B and Part C, the Viral Pharmacodynamic (PD) Set will be used for PD analysis and other Virology endpoint summaries.

Part A:

Day 29 is the primary readout timepoint and the end of study (EOS) analyses will be performed after all participants complete Week 24.

Part B and Part C:

Day 29 is the primary readout timepoint which will include primary and secondary endpoints defined through Day 8 and Day 29 and the end of study (EOS) analyses will be performed after all participants complete Week 36.

For this study, unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Data from Parts A, B and C will not be combined and reported in separate CSRs. Post CSR, PK data across parts and other VIR-7831 studies may be combined for a Population PK analyses.

4.1.2. Baseline Definition

For all endpoints (except PK, where the pre-dose sample will be used to confirm no drug effect in the body before administration of study intervention) the baseline value will be the latest pre-dose assessment with a non-missing value. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Baseline ECG definition (Part A, B and C):

The baseline ECG value will be defined as the average of the triplicate ECG assessments captured prior to dosing at Day 1. Similarly, 30 min post-dose ECG value will be defined as the average of the triplicate ECG assessments captured within 30 min of dosing at Day 1. These means of the triplicate QTcF assessments will not be rounded prior to categorisation as defined in Section 4.2.2.1.

Baseline Virology endpoint definition:

Baseline measurements for viral resistance surveillance and viral load is considered as nominal Day 1.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing. Participants with a missing baseline value will be excluded from the change from baseline analyses.

4.1.3. Multicenter Studies

It is anticipated that the summaries of data by center would unlikely be informative and will not, therefore, be provided.

4.1.4. Intercurrent Events

In general, the following may be considered intercurrent events/events leading to missing data if not part of the endpoint definition:

- Use of other COVID-19 therapy
- COVID-19 Vaccination (complete/incomplete vaccine series)
- Death

The intercurrent event handling strategies are described in Table 1 Estimands.

In general, the handling strategy of the intercurrent events for most of the endpoints will be a treatment policy strategy; specifically, the treatment effects will be estimated regardless of whether participants had experienced an intercurrent event or not. If possible, data will continue to be collected after the occurrence of the intercurrent event, until the participant either completes the study or withdraws from the study before completion.

Due to variations of COVID-19 Vaccines available to the subjects, including differences in number of required doses (i.e., 1 dose or 2 doses etc.), if a subject completes all required doses of the vaccine (e.g., 1/1 dose or 2/2 dose completely) will be considered under complete vaccine series group. Otherwise, if a subject takes partial dose will be considered under incomplete vaccine series group.

For some endpoints as listed in Table 1 Estimands strategies for intercurrent event of death will be composite.

Additional details on handling of missing data caused by any reason is described in Section 4.1.5.

4.1.5. Missing Data Handling Rules

Missing data can occur due to intercurrent events, study withdrawal or participants lost to follow-up before the completion of the study or due to intermittent missing values (i.e. data between two non-missing assessments). For Part A, missing data will not be imputed. However, for Part B and Part C, missing data will be handled as described below unless a modification of the strategy is required based on blinded data review during the study. Any changes in the algorithms will be documented appropriately prior to study database lock.

- The imputation logic when sample is reported as NEG or <2.08, impute 0.5 x 120 COPIES/ML = 60 COPIES/ML = 1.78 LOG COPIES/ML
- Subjects who die prior to Day 8 (or Day 5 or Day 11), their AUC viral load value will be imputed using the worst AUC viral load value from other subjects who have completed Day 8 (5/11) and have a valid AUC(D1-8)/(D1-5)/(D1-11).
- If Day 8 assessment alone is missing but Day 5 and Day 11 assessments are available, the Day 8 will be imputed using interpolation between Day 5 and Day 11. AUC will be calculated then.
- If either baseline and/or any of Day X (where X=5, 8, 11) viral loads are missing and cannot be interpolated using preceding and succeeding viral load values, then the corresponding AUC(D1-X) will be set to missing.
- If a subject lost to follow-up before Day 5, will be considered missing AUC(D1-8)/(D1-5)/(D1-11). More generally, if a subject is lost to follow-up prior to Day X, then AUC(D1-X) will be set to missing.

4.1.6. Exploratory Subgroup Analysis

For the virology endpoints for Part B and Part C, an exploratory subgroup analysis will be performed based on the baseline antibody status, if data permits.

4.2. Primary Endpoint Analysis

4.2.1. Definition of endpoint(s) by Parts

4.2.1.1. Part A

The primary analyses to evaluate safety and tolerability of VIR-7831 Gen 1 and Gen 2 treatments will be performed on the Safety Set.

The primary endpoints are:

- Occurrence of adverse events (AEs) through Day 29
- Occurrence of serious adverse events (SAEs) through Day 29
- Occurrence of adverse events of special interest (AESIs) through Day 29
- Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29
- Occurrence of disease progression events (not classified as AEs) through Day 29

For each endpoint mentioned above, the primary analysis will include all events with an onset date occurring on or before Day 29.

A data listing will contain all AEs and SAEs irrespective of the onset date, which will be presented both at the primary and end of study analyses.

Safety events occurring after Day 29 will be reported under Secondary objectives.

4.2.1.2. Part B and Part C

The primary endpoint is log_{10} transformed AUC of SARS-CoV-2 viral load from Day 1 to Day 8 ($AUC_{(D1-8)}$) as measured by qRT-PCR in NP swab samples. The Viral Pharmacodynamic set will be used.

For all intercurrent events, a treatment policy strategy will be used where data will be reported as captured. Missing virology data will be handled as described in Section 4.1.5.

4.2.2. Main analytical approach by Parts

4.2.2.1. Part A

A Treatment Policy Strategy will be considered for all possible intercurrent events where data will be reported as captured.

Adverse events through Day 29

An overview summary of AEs will be produced, including counts and percentages of participants with

- Any AE
    - All
    - AEs related to study intervention
    - AEs leading to permanent discontinuation of study intervention,
    - AEs leading to temporary interruption of study intervention
- Any Max Grade 3 and 4 AEs
    - All
    - AEs related to study intervention
    - AEs leading to permanent discontinuation of study intervention,
    - AEs leading to temporary interruption of study intervention
- Any SAE
    - All
    - SAEs related to study intervention,
    - fatal SAEs
    - fatal SAEs related to study intervention
- Any AESIs
    - All
    - AESIs related to study intervention
    - Fatal AESIs
    - Fatal AESIs related to study intervention

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the DAIDS 2017 v2.1.

Any AE and Any Max Grade 3 and 4 AEs

AEs by maximum severity will be presented.

The summary will use the following algorithms for counting the participant:

- Preferred term row: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- Any event row: Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate listings will also be provided for study intervention-related SAEs.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study intervention as “Yes” or missing.

A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing. The summary table will be displayed by PT only.

Any AESI

The following adverse events will be considered of special interest (AESI) and will be summarized using frequency and percentages separately.

- Infusion related reactions (IRR) including hypersensitivity reactions; reactions within 24 hours of start of infusion will be identified using a list of MedDRA codes confirmed by the Safety team.
- Immunogenicity (Anti-Drug Antibodies) related adverse drug reactions will be reported as a post-hoc summary after the end of the study. These potential events of ADAs will be detected by reviewing AEs that indicate HSR in those subjects who have positive anti-drug antibodies.
- Adverse events potentially related to antibody-dependent enhancement of disease (ADE) will be reported as a post-hoc summary after the end of the study. These potential events of ADEs will be detected by reviewing adverse event/serious adverse events for an increase in the incidence and severity of COVID complications for a participant that cannot be explained by underlying risk factors.

Additional AE summaries

- Most common AEs defined as any AE (PT) with an incidence of at least 5% in any of the treatment group will be summarized using frequency and percentages separately.

ECG findings through Day 29

A summary of the number and percentage of participants with newly occurring notable QTcF values, i.e.,

- post-baseline QTcF > 450, > 480, > 500 or
- QTcF increase vs BL >30, 60,
- any other ECG abnormalities up to Day 29 will be summarized by treatment.

The change from baseline (including worst case post-baseline assessment) in ECG parameters will be summarized by visit up to Day 29 using descriptive statistics. Participants with missing baseline values will be excluded from this summary of change from baseline. All ECG data will be listed.

Disease Progression Events (not classified as AEs) through Day 29

A summary of the number and percentage of participants with events related to expected progression, signs, or symptoms of COVID-19, unless more severe than expected for the participant's current clinical status and medical history will be provided. These events will be captured on the disease related event CRF and coded using MedDRA dictionary terms. This data will also be listed.

4.2.2.2. Part B and Part C

In Part B, the mean of log_{10} transformed $AUC_{(D1-8)}$ of SARS-CoV-2 viral load as measured by qRT-PCR in NP swab samples will be assessed using an Analysis of Covariance (ANCOVA) Model with treatments (IV and IM) and baseline viral load as covariates. The estimated geometric mean ratios and 90% CI of (500 mg IV:500 mg IM) after back-transformation will be presented.

In Part C, an additional randomization stratification factor (prior exposure to an authorized or approved SARS-CoV-2 vaccine) will be included in this ANCOVA model. The estimated geometric mean ratios and 90% CI of (250 mg IM:500 mg IV) after back-transformation will be presented.

Log_{10} transformed $AUC_{(D1-8)}$ of SARS-CoV-2 viral load will also be summarized descriptively using geometric mean, 95% confidence interval for the geometric mean, standard deviation of the log-transformed data (SD logs), between subject coefficient of variation ($\%CV_b$).

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoint(s) by Parts

4.3.1.1. Part A

The following secondary endpoints will be summarized in Part A.

Safety and Tolerability of VIR-7831 Gen 1 and Gen 2

The following safety data during the entire study period through Week 24, will be considered for safety analyses:

- Occurrence of non-serious AEs through Week 12
- Occurrence of SAEs through Week 24
- Occurrence of AESIs through Week 24

- Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12
- Occurrence of disease progression events (not classified as AEs) through Week 24

Change from baseline in viral load through Day 29

The change from baseline in viral load at all visits up until and including Day 29 is measured by qRT-PCR from saliva and/or nasal mid-turbinate swab samples. Additionally, to determine whether viral load in saliva is comparable to nasal mid-turbinate swab samples, correlation analysis will be performed to examine the relationship. This will be displayed overall and at all visits up until and including Day 29.

Pharmacokinetics of VIR-7831 Gen1 and Gen2

Serum pharmacokinetic concentrations and parameters will be listed and summarized by visit.

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin.

All calculations of non-compartmental parameters will be based on actual sampling times and will be listed and summarized using descriptive statistics. PK parameters may include, but not be limited to C_{max}, C_{last}, C_{D29}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, $AUC_{D1\text{-}D29}$, $\%AUC_{exp}$, $t_{1/2}$, V_z, V_{ss}, CL.

Inclusion of PK parameters in summaries will be at the discretion of the PK scientist. Any parameters not included in summaries should be flagged in the individual listings with an explanation for the exclusion.

Serum concentrations may be combined with data from other studies evaluating VIR-7831 for the purpose of population PK model development.

4.3.1.2. Part B and Part C

Safety and tolerability of VIR-7831 Gen2 administered via IV infusion and IM injection, through Day 29

The following endpoints will be evaluated for the Safety set:

- Occurrence of adverse events (AEs) through Day 29
- Occurrence of serious adverse events (SAEs) through Day 29
- Occurrence of adverse events of special interest (AESIs) through Day 29
- Occurrence of clinically significant abnormalities on 12-lead electrocardiogram (ECG) readings through Day 29
- Occurrence of disease progression events (not classified as AEs) through Day 29

For each endpoint mentioned above, the secondary analysis will include all events with an onset date occurring on or before Day 29.

Summary tables and listings containing all AEs and SAEs irrespective of the onset date will be presented both at the primary and end of study analyses.

Safety and Tolerability of VIR-7831 Gen2 administered via IV infusion and IM injection, through End of Study (EOS)

In addition, the following data during the entire study period be evaluated for the Safety set:

- Occurrence of non-serious AEs through Week 12
- Occurrence of SAEs through Week 36
- Occurrence of AESIs through Week 36
- Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12
- Occurrence of disease progression events (not classified as AEs) through Week 36

Effect of VIR-7831 Gen2 IV and Gen2 IM on the viral shedding profile in the upper respiratory tract

A. Change from baseline in viral load through Day 29

The change from baseline in viral load at all visits up until and including Day 29 as measured by qRT-PCR in NP swab samples will be summarized on the $\log_{10}$ scale. The Viral Pharmacodynamic set will be used. For all intercurrent events, a default treatment policy strategy will be considered.

B. Participants with undetectable viral load through Day 29

The proportion of participants with undetectable viral load at all visits up until and including Day 29 will be summarized based on the Viral Pharmacodynamic set. Participants who die before Day 29 will be considered to have not met the undetectable viral load status at all visit post the intercurrent event of death (Composite Strategy). For all other intercurrent events, data will be reported as captured.

C. AUC(D1-5) and AUC(D1-11) of SARS-CoV-2 viral load measured by qRT-PCR

The $\log_{10}$ transformed AUC of SARS-CoV-2 viral load from Day 1 to Day 5 ($AUC_{(D1-5)}$) and from Day 1 to Day 11 ($AUC_{(D1-11)}$) as measured by qRT-PCR in NP swab samples will be analysed similar to the primary PD endpoint. The Viral Pharmacodynamic set will be used.

The strategies for intercurrent events will be similar to the primary endpoint.

Effect of VIR-7831 Gen2 IV and IM on viral load clearance in the upper respiratory tract

Individuals with a persistently high viral load at Day 8

The proportion of participants with persistently high viral load at Day 8 will be summarized based on the Viral Pharmacodynamic set. A persistently high viral load will be defined based on VIR-7831 5001 (COMET-ICE) study data and will be documented appropriately prior to Day 8 analysis database release.

Participants who die before Day 8 will be considered to have met the persistently high viral load criteria at Day 8 (Composite Strategy). For all other intercurrent events, data will be reported as captured.

Pharmacokinetics of VIR-7831 Gen2 IV and IM

Serum pharmacokinetic concentrations and parameters will be listed and summarized by treatment and visit.

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times and will be listed and summarized using descriptive statistics.

PK parameters may include, but not be limited to C_{max}, C_{last}, C_{D29}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, $AUC_{D1\text{-}D29}$, $\%AUC_{exp}$, $t_{1/2}$, V_z (IV), V_{ss} (IV), CL (IV), V/F (IM), CL/F (IM), F (IM). For all intercurrent events, a Treatment Policy Strategy will be considered, where data will be reported as captured.

Inclusion of PK parameters in summaries will be at the discretion of the PK scientist. Any parameters not included in summaries should be flagged in the individual listings with an explanation for the exclusion.

Serum concentrations may be combined with data from other studies evaluating VIR-7831 for the purpose of population PK model development.
Data from Parts B and C of the study will be combined to determine the absolute bioavailability (F) based on the $\log_e$ transformed dose normalized AUC_{inf} for the IV (500 mg), IM (500 mg), and IM (250 mg). This will be analyzed using an analysis of covariance (ANCOVA) model with treatments (IV and IM) and weight as covariates. The estimated geometric mean ratios and 90% CI of (IM:IV) will be presented. In addition, dose proportionality in terms of extent and rate of exposure will be assessed based on the $\log_e$ transformed, dose normalized AUC_{inf}, AUC_{last}, $AUC_{D1\text{-}D29}$, and C_{max}. This will be achieved by performing an analysis of variance (ANOVA) on the dose normalized $\log_e$ transformed PK parameters from the IM treatments. The model will include the dose level as an independent variable. Estimates and 90% confidence intervals will be back transformed. Proportionality will be concluded if the 90% confidence interval of the dose-normalized geometric mean ratios (GMR) of AUC_{inf}, AUC_{last}, $AUC_{D1\text{-}D29}$, and C_{max} between the two dose levels fall between 0.8 and 1.25.

4.3.2. Main analytical approach by Parts

4.3.2.1. Part A

Safety and Tolerability of VIR-7831 Gen 1 and Gen 2

The secondary safety data will be summarized as described for Part A Primary Safety Analyses in Section 4.2.2.1

A Treatment Policy Strategy will be considered for all possible intercurrent events where data will be reported as captured.

Change from baseline in viral load through Day 29

The change from baseline in viral load at all visits up until and including Day 29 as measured by qRT-PCR from saliva and/or nasal mid-turbinate swab samples will be summarized on the log10 scale. The Virology Set (all participants with a central lab confirmed quantifiable nasal mid-turbinate and/or saliva swab sample at baseline) will be used.

For all other intercurrent events (as appropriate for this endpoint), a default treatment policy strategy will be considered.

Pharmacokinetics of VIR-7831 Gen1 and Gen2

Serum Pharmacokinetic concentrations and parameters will be summarized as described in Section 4.3.1.1.
For all intercurrent events, a Treatment Policy Strategy will be considered, where data will be reported as captured.

4.3.2.2. Part B and Part C

Safety and tolerability of VIR-7831 Gen2 administered via IV infusion and IM injection through Day 29

Adverse events through Day 29

Adverse events will be summarized as described in Section 4.2.2.1.

ECG findings through Day 29

A summary of the number and percentage of participants with newly occurring notable QTcF values, i.e.,

- post-baseline QTcF > 450, > 480, > 500 or
- QTcF increase vs BL >30, 60,
- any other ECG abnormalities up to Day 29 will be summarized by treatment.

The change from baseline (including worst case post-baseline assessment) in ECG parameters will be summarized by visit up to Day 29 using descriptive statistics. Participants with missing baseline values will be excluded from this summary of change from baseline. All ECG data will be listed.

Disease Progression Events (not classified as AEs) through Day 29

A summary of the number and percentage of participants with events related to expected progression, signs, or symptoms of COVID-19, unless more severe than expected for the participant's current clinical status and medical history will be provided. These events will be captured on the disease related event CRF and coded using MedDRA dictionary terms. This data will also be listed.

4.3.2.3. Safety and Tolerability of VIR-7831 Gen2 administered via IV infusion and IM injection, through End of Study (EOS)

For this secondary objective the safety data below:

- Occurrence of non-serious AEs through Week 12
- Occurrence of SAEs through Week 36
- Occurrence of AESIs through Week 36
- Occurrence of clinically significant abnormalities on 12-lead ECG readings through Week 12
- Occurrence of disease progression events (not classified as AEs) through Week 36

will be summarized as described in Section 4.2.2.1, but over the entire study period (i.e., Day 1 to Week 36), except non-serious AEs which will be reported up until and including Week 12.

4.3.2.4. Change from baseline in viral load through Day 29

The change from baseline in viral load at all visits up until and including Day 29 as measured by qRT-PCR from NP swab samples will be summarized descriptively on the log_{10} scale.

4.3.2.5. Participants with undetectable viral load at all visits through Day 29

The proportion of participants with undetectable viral load at all visits up to and including Day 29 will be summarized using frequency and percentages.

4.3.2.6. $AUC_{(D1-5)}$ and $AUC_{(D1-11)}$ of SARS-CoV-2 viral load measured by qRT-PCR

The $AUC_{(D1-5)}$ and $AUC_{(D1-11)}$ of SARS-CoV-2 viral load measured by qRT-PCR will be summarized descriptively and analyzed using a similar ANCOVA model as described in the Primary analysis Section 4.2.2.

4.3.2.7. Individuals with a persistently high viral load at Day 8

The proportion of participants with persistently high viral load at Day 8 will be summarized using frequency and percentages.

4.3.2.8. Pharmacokinetics of VIR-7831 Gen2 IV and IM

Serum pharmacokinetic concentrations and parameters will be summarized as described in Section 4.3.1.2. For all intercurrent events, a Treatment Policy Strategy will be considered, where data will be reported as captured. Absolute bioavailability and dose proportionality will be assessed as described in Section 4.3.1.2

4.3.3. Subgroup Analyses

For Part C, a summary of subgroup by IM injection site location (deltoid muscle vs gluteal muscle) will be performed on the secondary endpoint of overall AEs detailed in Section 4.3.1.2. The corresponding listing will include additional details of injection site location such as right/left/unknown, ventral/dorsal/unknown.

4.4. Exploratory Endpoints Analyses in Parts A, B and C

4.4.1. SARS-CoV-2 resistant mutants against VIR-7831

This endpoint describes presence at baseline and on-treatment emergence of SARS-CoV-2 resistant mutants against VIR-7831 in subjects based on the Safety set. The data will be reported as captured (Treatment Policy Strategy).

The frequency and percentage of subjects who have resistance mutations will be summarized. Subject listings of viral variants detected in the spike gene by next generation sequencing will be provided. Additional data may also be summarized based on emerging data from COMET-ICE study and will be documented in the OPS document.

Phenotypic analysis will be performed in vitro and will be summarized in a separate report.

4.4.2. Incidence and titers of serum ADA to VIR-7831

The incidence and titers (if applicable) of serum ADA to VIR-7831 will be summarized using frequency counts by treatment and visits up to Week 24.

4.4.3. Determination of anti-N, anti-S and anti-RBD SARS CoV-2 antibodies at baseline to investigate effect of immune status on response

The incidence and titers (if applicable) of anti-N, anti-S and anti-RBD SARS CoV-2 antibodies at baseline will be summarized using frequency counts by treatments (including a total column). For the virology endpoints, an exploratory subgroup analysis will be performed based on the baseline antibody status, if data permits.

4.4.4. Determination of anti-N SARS CoV-2 antibodies at Day 29 to investigate effect of VIR-7831 treatment on development of immunity

The incidence and titers (if applicable) of anti-N SARS CoV-2 antibodies at Day 29 will be summarized using frequency counts by treatments (including a total column).

4.5. Other Safety Analyses

The following safety analyses will be based on the Safety Set.

4.5.1. Extent of Exposure

4.5.1.1. Part A, Part B and Part C

Summary and listing of exposure by participants presenting the number of participants exposed and the number of participants with interruptions or infusion stopped early and not completed will be presented.

4.5.2. Laboratory Data

Summaries by shift tables of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DAIDS 2017 v2.1. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized by visit along with any increase to a maximum grade of 2 or 3 or 4. Missing baseline grade will be assumed as grade 0 (Normal).

For laboratory tests with both low and high values as per lab normal ranges, summaries will be provided separately and labelled by direction.

For lab tests that are not gradable by DAIDS 2017 v2.1, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

For Part A, only listings for hematology, and chemistry laboratory tests will be produced and change from baseline summaries will not be produced due to small sample size. For Part B and Part C, summaries of change from baseline and listings for hematology, and chemistry laboratory tests will be produced separately. Liver function laboratory tests will be included with chemistry lab tests in each Part.

In all Parts of the study, separate summary of hepatobiliary laboratory events (if any) including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's Law case:

- ALT ≥ 3xULN AND total bilirubin ≥ 2xULN (≥ 35% direct bilirubin) or international normalized ratio (INR) >1.5
- Alkaline phosphatase (ALP) < 3×ULN/missing.
- Total bilirubin ≥ 2×ULN can be within 29 days following the ALT elevation and if direct bilirubin is available on the same day, it must be > 35% of total bilirubin.
- ALP < 2×ULN/missing means it is satisfied unless the ALP is ≥ 2xULN at the time of bilirubin elevation.

The summary will be produced for worst case post baseline only. For Part B and Part C, a plot for maximum post-baseline Total Bilirubin against ALT will also be produced and will be repeated with the values standardized with respect to baseline, instead of ULN. This is to account for the individual variation at baseline.

4.5.3. Vital Signs

Summaries of grade increase and/or decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately using shift tables for each of Parts A, B and C. These summaries will display the number and percentage of participants with shift by any grade increase and /or decrease including worst case post-baseline.

The grade definitions for SBP and DBP are:

Vital Sign Parameter	Units	Clinical Grade Range			
		Grade 0	Grade 1	Grade 2	Grade 3
Systolic Blood Pressure	mmHg	<120	120-139	140-159	>=160
Diastolic Blood Pressure	mmHg	<80	80-89	90-99	>=100

In addition, summaries using standard descriptive statistics of change from baseline in vital signs parameters (blood pressure, respiratory rate, heart rate and temperature) by visit will be provided for Part B and Part C only. In all Parts of the study, a boxplot will be presented for blood pressures by treatment. A summary of temperature will also be presented by timepoints as "Day 1" and > "Day 1" and pre-defined categories i.e., <38ºC, 38ºC-<38.4ºC, 38.4ºC-<38.9ºC, 38.9ºC-<40ºC and >=40ºC.

In addition, listings of vital signs parameters (blood pressure, respiratory rate, heart rate and temperature) by visit will be provided.

4.5.4. Oxygen Saturation

Summaries of actual and changes in blood oxygen saturation (SpO2) and proportion of participants administered oxygen at each visit will be provided separately for each of Parts A, B and C. Summaries of worst-case actual changes in Fraction of Inspired Oxygen (FiO2) and SpO2/FiO2 ratios will be summarized for those administered supplemental oxygen.

Respiratory support is documented according to the following categories:

1. Low-flow nasal cannula/prongs
2. High-flow oxygen therapy (including Face mask with reservoir)
3. Low-flow oxygen mask
4. CPAP (continuous positive airway pressure)
5. BIPAP (bilevel positive airway pressure)
6. Invasive mechanical ventilation
7. ECMO (extracorporeal membrane oxygenation)

Changes in requirement for respiratory support/ventilation procedures (listed above) will be summarized using proportions of participants with change from baseline to higher respiratory support in each category by visit.
In addition, the proportion of participants in each category will be summarized at each visit using a stacked bar chart.

Individual participant profiles showing the time course of respiratory support/ventilation procedures will also be produced.

4.6. Interim Analyses

No interim analyses will be conducted in this study.
However, in each Part, once the last participant recruited completes the primary assessment, the data will be analyzed for a readout of the primary and selected secondary endpoints. Data from different Parts of the study will not be combined for analysis and separate study reports will be prepared, as appropriate. Participants will continue to complete the remaining scheduled assessments till the end of study (EOS) at Week 24(for Part A)/Week 36 (for Part B and C).

4.7. Changes to Protocol Defined Analyses

This SAP is aligned to the Protocol Amendment 05 dated 29/10/2021.

5. SAMPLE SIZE DETERMINATION

5.1. Part A Sample Size Determination

Approximately 40 participants will be randomized in a 3:1 ratio to VIR-7831 Gen2 or Gen1 material.
The sample size is based on practical considerations, i.e., experience with similar types of studies that allow for reasonable qualitative data. No formal sample size calculations were performed; however, a sample size of 40 subjects (30 Gen2, 10 Gen1) should provide suitable assessment of the descriptive safety, tolerability and PK profile for VIR-7831 Gen2. Table 2 shows examples of the precision in the estimated AE rate on the Gen2 arm. A decision to stop recruitment after enrolment of 30 participants was made due to:

- The absence of serious safety concerns noted at the 13 May 2021 Joint Safety Review Team (JSRT) review of the 30 participants enrolled in Part A
- The significant clinical experience gained with use of Gen2 IV material (500 mg) in the BLAZE-4 study in the early treatment population (approximately 100 participants received Gen2 VIR-7831)
- PK samples collected for the current 30 participants for Part A are expected to compliment other PK data from the BLAZE-4 study to assess PK endpoints for Gen2 VIR-7831

Table 2 Precision in the Estimated AE Rate (Gen2) for Part A

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

5.2. Part B Sample Size Determination

Approximately 150 participants will be randomized in a 1:1 ratio to VIR-7831 Gen2 IV or IM. The sample size is based on enabling a comparison of log10 SARS-CoV-2 viral load AUC(D1-8) following a single dose of 500 mg IV or a single dose of 500 mg IM that will be made based on the treatment ratio 90% confidence interval falling within pharmacological equivalence bounds of 0.5 to 2.0 and assumed coefficient of variation of 200% and the true ratio is 1. The margin of 0.5 to 2.0 is deemed appropriate for the comparison of viral load due to the endpoint being a variable PD endpoint. Table 3 presents the sensitivity of power for different values of coefficient of variations, given the same sample size of 75 participants per arm.

Table 3 Sample Size Sensitivity Assessment for Part B

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

5.3. Part C Sample Size Determination

Approximately 150 participants will be randomized in a 1:1 ratio to VIR-7831 Gen2 500 mg IV or 250 mg IM. The sample size is based on enabling a comparison of log10 SARS-CoV-2 viral load AUC(D1-8) following a single dose of 500 mg IV or a single dose of 250 mg IM that will be made based on the treatment ratio 90% confidence interval falling within pharmacological equivalence bounds of 0.5 to 2.0 and assumed coefficient of variation of 200% and the true ratio is 1. The margin of 0.5 to 2.0 is deemed appropriate for the comparison of viral load due to the endpoint being a variable PD endpoint. Table 4 presents the sensitivity of power for different values of coefficient of variations, given the same sample size of 75 participants per arm.

Table 4 Sample Size Sensitivity Assessment for Part C

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

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Term	Definition
ADA	anti-drug antibodies
ADE	antibody dependent enhancement
AE	adverse event
AESI	adverse event of special interest
ALT	Alanine Aminotransferase
AUC_{inf}	area under the plasma concentration-time curve extrapolated to infinite time
AUC_{last}	area under the curve from the time of dosing to the time of the last measurable (positive) concentration
$\%AUC_{exp}$	the extrapolated portion of AUC_{inf}
$AUC_{D1\text{-}D29}$	area under the plasma concentration-time curve, from study Day 1 to Day 29
BMI	body mass index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
C_{last}	Observed concentration corresponding to t_{last}.
C_{max}	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CV	Cardiovascular
DAIDS	Division of acquired immune-deficiency syndrome
DP	Drug Product
DS	Drug Substance
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EU	European Union
FcγR	Fc Gamma Receptor

Term	Definition
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
HSR	Hypersensitivity reactions
IB	Investigator's brochure
ICF	Informed consent form
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IRR	Infusion related reaction
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous
JSRT	Joint safety review team
LAR	Legally authorized representative
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material safety data sheet
NP	Nasopharyngeal
NQ	Non-quantifiable
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
QTLs	Quality tolerance limits
RBC	Red blood cell count
RNA	Ribonucleic acid

Term	Definition
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SoA	Schedule of activities
SoC	Standard of care
SpO2	Oxygen saturation
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal elimination half-life
t_{last}	Time of the last quantifiable concentration
t_{max}	Time to reach C_{max}
UK	United Kingdom
ULN	Upper limit of normal
US	United States
V	Variance
Vir	Vir Biotechnology, Inc.
V_{ss}	The volume of distribution at steady state
V_z	Apparent volume of distribution during the elimination
WHO	World Health Organization
λz	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve.

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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7. REFERENCES

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