SPONSOR SIGNATURE PAGE

STUDY TITLE: A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2 Platform Study to Determine the Phase 2a dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19 (Candidate Specific Trial Protocol 5 [CST-5])

Study: 215337 (CST-5) Development Phase: 1/2a

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Karen Jennings-Wilding

Title of Sponsor Signatory: Senior Clinical Research Governance Manager

University of Liverpool

Signature:

DocuSigned by:
Karen Jennings-Wilding
Signer Name: Karen Jennings-Wilding
Signing Reason: I approve this document
Signing Time: 21 February 2024 | 10:10:19 AM GMT
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Date: 21 February 2024

INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2 Platform Study to Determine the Phase 2a dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19 (Candidate Specific Trial Protocol 5 [CST-5])

I have read this report and confirm that to the best of my knowledge Study 215337 (CST-5) was carried out as described in this GSK Report

Name of Investigator:	Dr. Richard Fitzgerald
Affiliation:	Director of the Clinical Research Facility University of Liverpool
Signature of Investigator:	DocuSigned by: Signer Name: Richard Fitzgerald Signing Reason: I approve this document Signing Time: 21 February 2024 | 5:26:44 PM GMT B111811D3E204666B7DA9B4358793F28
Date:	21 February 2024

Division: Worldwide Development
Information Type: Abbreviated Clinical Study Report
Control: placebo

Title:	A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2 Platform Study to Determine the Phase 2a dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19 (CST-5)
Phase:	1/2a
Compound:	VIR-7832 (GSK4182137) and VIR-7831 (sotrovimab; GSK4182136; Xevudy™)
Document Date:	04 March 2024

Subject: COVID-19

Indication Studied: Treatment of COVID-19

Initiation Date:	20 April 2021
Completion Date:	13 January 2023

Sponsor Signatory: (and Medical Officer)	Dr. Richard Fitzgerald Director of the Clinical Research Facility University of Liverpool

This study was performed in compliance with the principles of Good Clinical Practices and University of Liverpool/AGILE/SCTU Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AUC	Area under the curve
$AUC_{(D1-8)}$	Area under the curve from Day 1 to Day 8
$AUC_{(D1-29)}$	Area under the curve from Day 1 to Day 29
AUCinf	Area under the plasma concentration-time curve extrapolated to infinite time
%CVb	between-subject coefficient of variation
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed concentration
COVID	Coronavirus disease
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CST-5	Candidate Specific Trial Protocol 5
CTD	Common Technical Document
DLT	Dose limiting toxicity
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
ICH	International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
ITT	Intent-to-treat
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
OPS	Output and Programming Specification
PCR	Polymerase Chain Reaction
Ph	Phase
PI	Principal Investigator
PID	Participant Identifiable Data
PK	Pharmacokinetics
PT	Preferred term
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
QTLs	Quality tolerance limits
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trial Unit
SOC	System organ class

SOP	Standard Operating Procedure
SRC	Safety Review Committee
VEO	Value Evidence Outcomes
Vir	Vir Biotechnology
Vss	Volume of distribution
WHO	World Health Organization

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ETHICS AND GOOD CLINICAL PRACTICE

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the principles of ICH GCP and applicable country-specific requirements, for constitution of independent ethics committees. Ethics committee or institutional review board approvals are maintained in the Sponsor's study file. AGILE-CST5 was added to the AGILE platform by Amendment 8, this was reviewed by West Midlands - Edgbaston Research Ethics Committee and approved by this ethics committee on 20 January 2021.

Investigators were trained to conduct the study in accordance with the principles of GCPs and the study protocol, as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to conduct the study in accordance with the principles of ICH GCP and all applicable participant privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki, and to conduct the study in accordance with the protocol.

Monitoring mitigations were deployed as COVID-19 restrictions prevented on-site monitoring. These included QC of data by Liverpool staff, remote calls, remote monitoring of consent forms and central monitoring of the database. If significant findings (e.g., potential serious misconduct or noncompliance with GCP, including potential Serious Breaches) were identified during monitoring or auditing of a site, these are presented in Section 5.2, Protocol Deviations, of this report.

Written informed consent was obtained from each participant prior to the performance of any study-specific procedures. The investigator agreed to provide the participant as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study participant and by the person who conducted the informed consent discussion. Case report forms were provided for each participant's data to be recorded. The study was conducted per the Standard Operating Procedures of the University of Liverpool/Southampton Clinical Trial Unit (SCTU).

Synopsis

Name of company: Vir Biotechnology and GSK Research & Development Limited

Name of finished product: Sotrovimab

Name of active substance: VIR-7832 (GSK4182137) and VIR-7831 (sotrovimab; GSK4182136)

Study Number: 215337

Title: A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2 Platform Study to Determine the Phase 2a dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19 (Candidate Specific Trial Protocol 5 [CST-5])

Investigator(s):

Study center(s): Multicenter

Publication(s): None

Study Period: 20 April 2021 to 13 January 2023

Phase of Development: 1/2a

Objectives:

Primary Objective:	Phase 1: • To determine the safety and tolerability of single doses of VIR-7832, to aid dose selection for Phase 2a Phase 2a: • To investigate the effect of VIR-7832 compared with placebo on SARS-CoV-2 viral load
Secondary Objectives:	Phase 1: • To characterize the Pharmacokinetics (PK) of single doses of VIR-7832 Phase 2a: • Safety Objective: To determine the safety and tolerability of single doses of VIR-7832 and VIR-7831 • To characterize the PK of single doses of VIR-7832 and VIR-7831 • To investigate the effect of VIR-7832 and VIR-7831, both compared with placebo, on SARS-CoV-2 viral load over time • To evaluate time to, and proportion of participants with clinical improvement

Exploratory Objectives:	Phase 1: • To investigate the exposure-response relationship of the VIR-7832-mediated effect on SARS-Cov-2 viral dynamics Phase 2a: • To compare the effect of VIR-7832 versus VIR-7831 on T-cell responses to SARS-CoV-2 • To investigate the clinical efficacy of VIR-7832 • To monitor for SARS-CoV-2 resistance mutations against VIR-7831 and VIR- 7832 • To evaluate the effect of VIR-7832 and VIR-7831 versus placebo on potential biomarkers of host response to SARS-CoV-2

Methodology:

This was a 3:1 randomized, blinded, placebo-controlled phase 1 study of VIR-7832 (GSK4182137) versus placebo, followed by a 2:2:1 blinded, parallel group Phase 2a study of VIR-7832 versus VIR-7831 versus placebo. A phase 1 was carried out to test the safety and tolerability of VIR-7832. Following review of safety and tolerability data from evaluated doses of VIR-7832, a dose (500 mg) was selected to progress to phase 2a. The selected dose of VIR-7832 was further evaluated in a blinded, placebo-controlled randomized Phase 2a study, which assessed the safety and virological efficacy of VIR-7832 and VIR-7831.

Number of participants:

A total of 36 participants (24 in Phase 1 and 12 in Phase 2a) were enrolled and 34 (94%) participants completed the study.

Diagnosis and main criteria for inclusion:

Adults (18 years to 65 years in Phase 1; ≥18 years in Phase 2a) with laboratory-confirmed SARS-CoV-2 infection (PCR).

Group B (mild-moderate disease): Ambulant participants with peripheral capillary oxygen saturation (SpO2) and >94% Room Air (RA) and who have experienced symptoms of COVID-19 for ≤168 h (7 days).

Participants were required to have COVID-19 defined by 1 or more of the following symptoms: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhoea, shortness of breath on exertion, that began within 7 days of the planned dose of study drug. Within 7 days was defined as Day 0 being the symptom onset day and Day 7 being the last treatment day possible.

Treatment administration:

Phase 1:

Single doses of VIR-7832 were administered by intravenous (IV) infusion over 1 hour. The starting dose was 50 mg, and dose escalations of 150 and 500 mg were performed, with escalation guided by emerging safety data and decision by the Safety Review Committee (SRC). Participants were monitored for 253 days post-dose (36 weeks) in line with the expected long half-life of VIR-7832.

Phase 2a:

A VIR-7832 dose of 500 mg was selected based on the safety and tolerability data from Phase 1. All treatments were given by IV infusion over 1 hour.

Criteria for evaluation:

Primary Study Endpoints:	Phases I: • Adverse events and serious adverse events • Dose limiting toxicities (Safety and Tolerability of VIR-7832 - CTCAE v5 Grade 2:3 adverse events) up to day 8 Phase 2a: • Change from baseline to Day 8 in SARS-CoV-2 viral load
Secondary Study Endpoints:	Phase 1: • PK parameters of VIR-7832 up to Day 169 (Week 24) Phase 2a: • Adverse events and serious adverse events, physical findings, vital signs and laboratory parameters • PK parameters ofVIR-7832 and VIR-7831 up to Day 169 (Week 24) • Change from baseline over time, up to Day 29, in viral load • Time to negative viral titres (Day 1-29) • Proportion of participants with clinical improvement (as defined above) at day 8, 15 and day 29. • Change at day 8 and 15 from randomization in the WHO Clinical Progression Scale. • Time to a one point change on the WHO Clinical Progression Scale
Exploratory endpoints:	Phase 1: • The effect of dose on viral dynamics Phase 2a: • Change from baseline over time, up to Day 29, in SARSCoV2 specific T-cells frequencies in blood • Proportion of participants who have progression of COVID-19 as defined by hospitalization (WHO scale Grade 4-9) >24 hrs or death (WHO scale Grade 10) at Day 8, Day 15, Day 22, or Day 29 • Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifested by the requirement for and method of supplemental oxygen (WHO scale Grades 5-9) at Day 8, Day 15, Day 22, or • Day 29

	• Severity of participant-reported symptoms of COVID-19-related illness using the Flu-PRO participant-reported outcome instrument (Days 1 to 15, Day 22 and Day 29) • Frequency of SARS-CoV-2 resistance mutations against VIR-7831 and VIR-7832, up to Day 29 • Host immune responses and exploratory biomarkers related to SARS-CoV-2, VIR-7831and/or VIR-7832, including genetic, cellular, transcriptomic, and proteomic parameters (including anti-SARS-CoV Nucleocapsid [N] antibody)

Statistical methods:

Phase 1:

Participants were randomized in phase 1, 3:1 to treatment and placebo, with the first 2 participants in each cohort randomized 1:1. Fewer than 3 cohorts and up to 32 participants (4 cohorts of 8 participants) could have been enrolled, with the final number dependent on dose escalation decisions. Each cohort included 6 VIR-7832 and 2 placebo treated participants.

Phase 2a:

A total of 125 additional participants were planned to be randomized in a 2:2:1 ratio to VIR-7832, VIR-7831 and placebo. Participants who were randomized to placebo or the selected phase 2a dose of VIR-7832 in phase 1 were included in the analysis of phase 2a.

Summary:

This study was stopped early after the enrollment of 12 participants in Phase 2a due to changes in the susceptibility of emerging SARS-CoV2 variants to the study drugs.

Participants in each treatment group completed the study through Week 36 except for 2 participants in the Ph1 VIR-7832 50 mg treatment group. The majority (92%) of participants were white. Mean age for all treatment groups ranged from 28.5 to 52.8 years. All participants received the full dose of infusion. No participants discontinued the treatment early.

Most (35 [97%]) participants reported AEs, of which 5 events (non-serious) were considered related to study treatment in 5 (14%) participants. Three (8%) participants reported 7 SAEs, none of which were fatal or related to study treatment. There were no AEs leading to permanent discontinuation of study treatment or dose interruption/delay. Changes in laboratory and vital sign parameters were consistent with baseline conditions and underlying COVID-19 disease. One participant in the Ph1 VIR-7832 (150 mg) treatment group experienced a dose-limiting toxicity (DLT) of Grade 3 syncope 1 day after dosing that lasted 1 day and was judged not related to study treatment by the investigator.

Following IV administration of VIR-7832 50 mg, 150 mg, and 500 mg, the geometric mean C_{max} was 16.8 (n=6, $\%CV_b$ = 15.56) µg/mL, 52.9 (n=6, $\%CV_b$ = 13.74) µg/mL, and 176.1 (n=9, $\%CV_b$ = 9.73) µg/mL, respectively. Following IV administration of VIR-7831 500 mg, the geometric mean C_{max} was 182.7 (n=5, $\%CV_b$ = 12.65) µg/mL.

The geometric mean AUC_{inf} was 475.5 (n=5, $\%CV_b$ =7.87) µg/mL, 1811.2 (n=5, $\%CV_b$ = 16.80) µg/mL, and 4843.4 (n=9, $\%CV_b$ = 6.83) µg/mL following IV administration of VIR-7832 50 mg, 150 mg, and 500 mg, respectively. The geometric mean AUC_{inf} was 5525.7 (n=5, $\%CV_b$ = 59.49) µg/mL following IV administration of VIR-7831 500 mg.

The geometric mean of the estimated steady state volume of distribution (Vss) and clearance (CL) were 5.85-6.85 L and 82.8-105.2 mL/day for VIR-7832, and 6.39 L and 90.5 mL/day for VIR-7831, respectively. The median half-life was 40.7-49.9 days for VIR-7832 and 61.5 days for VIR-7831.

There was no apparent impact of ADA on VIR-7831/VIR7832 exposure or safety.

In Phase 1, participants receiving 50, 150 or 500 mg VIR-7832 (N=6 at each dose) had median baseline viral loads of 2.491 to 4.012 log_{10} copies/mL and a median change in viral load of -2.491 to -3.889 log_{10} copies/mL observed at Day 29. In Phase 2a, participants receiving 500 mg VIR-7832 (N=4) had a median baseline viral load of 7.257 log_{10} copies/mL and median change from baseline viral load -7.257 log_{10} copies/mL at Day 29. In Phase 1, all participants receiving 50, 150 and 500 mg VIR-7832 (N=6 per dose group) achieved negative viral titers by Day 15, Day 8 and Day 8, respectively. In Phase 2a, all participants receiving 500 mg VIR-7832 (N=4) achieved negative viral titer at Day 15. The geometric mean $AUC_{(D1-8)}$ for participants receiving 50, 150 and 500 mg VIR-7832 in Phase 1, ranged from 4.61 to 7.18, as compared to that of the participants receiving placebo which was 19.91. The geometric mean $AUC_{(D1-8)}$ for participants receiving 500 mg VIR-7832 in Phase 2a was 26.32 as compared that of participants receiving placebo (15.35) or VIR-7831 (16.69).

There was a mean trend decrease (with observed variability) over time in WHO Clinical Progression Score, and the decreases were similar between treatment and placebo groups, indicating a decrease in illness severity over time. There was a decrease over time in all treatment groups for FLU-PRO Total Score, indicating decrease in severity of symptoms. There were no COVID-19 progressions.

Conclusions:

Safety

- The safety data from this study suggest a favorable tolerability profile of VIR-7832 (GSK4182137) and VIR-7831 (sotrovimab; GSK4182136) in adult participants for treatment of COVID-19.

PK

- The geometric mean of the estimated steady state volume of distribution ranging 6-7 L for VIR-7832 indicates limited distribution outside the vascular space, which is consistent with other IgGs. The long half-life (40-50 days) observed for VIR-7832 is consistent with the addition of the half-life extending LS mutation.
- Exposures following 500 mg and 150 mg IV VIR-7832 were approximately 10x and 3x the exposure observed following 50 mg IV dose of VIR-7832, respectively, which indicates dose proportionality over the dose range of 50-500 mg. However, formal dose proportionality analysis was not performed.

Immunogenicity

- There was no apparent impact of ADA on VIR-7831or VIR7832 exposure or safety.

Virology

- The levels of SARS-CoV-2 RNA decreased over time for participants receiving VIR-7832 in Phase 1 and Phase 2a.
- All participants receiving VIR-7832 in Phase 1 or Phase 2a achieved negative viral titer by Day 15.
- The geometric mean $AUC_{(D1-8)}$ and $AUC_{(D1-29)}$ of SARS-CoV-2 viral load was similar for participants receiving 50, 150 and 500 mg VIR-7832 in Phase 1.
- Comparisons for absolute viral load, change from baseline in viral load, time to negative viral titer and AUC for viral load between VIR-7832 dose groups and participants receiving placebo or comparator (VIR-7831) were not done due to small numbers of participants and differences in baseline viral load in each group.

Clinical

- A beneficial effect of VIR-7832 or VIR-7831 cannot be evaluated due to the lack of progression to severe disease and the small sample size of the study.

Document Date: 01 March 2024

1. INTRODUCTION

In December 2019, SARS-CoV-2, a novel betacoronavirus, was first reported to cause severe pneumonia in Wuhan, China and subsequently had a rapid spread around the world. As of 31 December 2023, over 773 million cases of COVID-19 and over 7 million associated deaths have been reported globally, and over 103.4 million cases including over 1.2 million deaths have been reported in the US [WHO, 2024].

VIR-7832 is a human IgG1 kappa (IgG1κ) monoclonal antibody (mAb) derived from the parental mAb S309, a potent neutralizing mAb directed against the spike protein of SARS-CoV-2 (Pinto 2020). The Fc region of the molecule contains the LS and XX2 modifications. The LS modification is designed to increase half-life [Aweda, 2023; Ko, 2014; Zalevsky, 2010; Gaudinski, 2018; Hope, 2019]. The XX2 modification imparts enhanced effector functions, abrogates C1q binding, and has the potential for amplifying T-cell responses (Weitzenfeld 2019), which may provide for increased potency and induce a "vaccinal" effect via the potential enhancement of T-cell responses. While both VIR-7832 and sotrovimab have identical Fab regions, sotrovimab only has the LS modification, and there is no XX2 modification to the Fc region. VIR-7832 and sotrovimab bind with high affinity to the receptor binding domain of the SARS-CoV-2 spike protein. VIR-7832 neutralizes SARS-CoV-2 virus wild-type (WA1 isolate) in vitro with an EC50 of 78.3 ng/mL and effectively neutralizes pseudotyped virus containing the wild-type SARS-CoV-2 spike protein.

Sotrovimab neutralizes SARS-CoV-2 authentic virus and pseudotyped virus and has retained activity against many variants of concern and interest (VOC/VOI) of the SARS-CoV-2 virus [Addetia, 2023; Aweda, 2023; Cathcart 2022; Park, 2022].

Sotrovimab has been demonstrated to reduce hospitalization and/or death by 79% in non-hospitalized participants with mild to moderate COVID-19 who are at risk of progressing to severe disease when administered IV within 7 days of infection in a Phase 3 early treatment study COMET-ICE (Study VIR-7831-5001/GSK Study 214367) [Sotrovimab, 2022; Gaudinski 2018; Gupta, 2021; Gupta, 2022]. The COMET-ICE study was conducted when the dominant form of the coronavirus was the original Wuhan strain.

Phase 1 of this AGILE study comprised a first-time-in-human, dose-escalation phase for VIR-7832, in which participants were randomized to VIR-7832 or placebo in a 3:1 allocation ratio. Each of these cohorts were double-blind and blinded safety data was reviewed between cohorts by the SRC. Based on review of safety and tolerability data from evaluated doses, a 500 mg dose of VIR-7832 was selected to progress to phase 2a, which intended to evaluate VIR-7832, VIR-7831 and placebo in a 2:2:1 ratio. The primary aim of this study was to assess the safety, tolerability and virological efficacy of VIR-7832 compared with placebo. The study also planned to assess:

1) Additional benefit of the "XX2" modification associated with VIR-7832, by comparing T cell responses between VIR-7832 and VIR-7831
2) Clinical efficacy of VIR-7832 compared with placebo

3) Safety, tolerability and virological efficacy of VIR-7832 compared with placebo
4) PK, resistance potential and effect on potential biomarkers of host response for VIR-7832 and VIR-7831.

Additional introductory and background details are provided in the study protocol, Section 2.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

Objectives	**Endpoints**
Primary Objective: Phase 1: • To determine the safety and tolerability of single doses of VIR-7832, to aid dose selection for Phase 2a Phase 2a: • To investigate the effect of VIR-7832 compared with placebo on SARS- CoV-2 viral load	Primary Study Endpoints: Phases I: • Adverse events and serious adverse events • Dose limiting toxicities (Safety and Tolerability of VIR-7832 - CTCAE v5 Grade ≥3 adverse events) up to day 8 Phase 2a: • Change from baseline to Day 8 in SARS-CoV-2 viral load
Secondary Objectives: Phase 1: • To characterise the Pharmacokinetics (PK) of single doses of VIR-7832 Phase 2a: • Safety Objective: To determine the safety and tolerability of single doses of VIR-7832 and VIR-7831 • To characterise the PK of single doses of VIR-7832 and VIR-7831 • To investigate the effect ofVIR-7832 and VIR-7831, both compared with placebo, on SARS-CoV-2 viral load over time Clinical Objective: To evaluate time to, and proportion of participants with clinical improvement	Secondary Study Endpoints: Phase 1: • PK parameters ofVIR-7832 up to Day 169 (Week 24) Phase 2a: • Adverse events and serious adverse events, physical findings, vital signs and laboratory parameters • PK parameters ofVIR-7832 and VIR-7831 up to Day 169 (Week 24) • Change from baseline over time, up to Day 29, in viral load • Time to negative viral titres (Day 1-29) • Proportion of participants with clinical improvement (as defined above) at day 8, 15 and day 29. • Change at day 8 and 15 from randomization in the WHO Clinical Progression Scale. • Time to a one point change on the WHO Clinical Progression Scale

Exploratory Objectives:	Exploratory endpoints:
Phase 1: • To investigate the exposure-response relationship of the VIR-7832- mediated effect on SARS-CoV-2 viral dynamics Phase 2a: • To compare the effect of VIR-7832 versus VIR-7831 on T-cell responses to SARS-CoV-2 • To investigate the clinical efficacy of VIR-7832 • To monitor for SARS-CoV-2 resistance mutations against VIR-7831 and VIR-7832 • To evaluate the effect of VIR-7832 and VIR-7831 versus placebo on potential biomarkers of host response to SARS-CoV-2	Phase 1: • The effect of dose on viral dynamics Phase 2a: • Change from baseline over time, up to Day 29, in SARSCoV2 specific T-cells frequencies in blood • Proportion of participants who have progression of COVID-19 as defined by hospitalization (WHO scale Grade 4-9) >24 hrs or death (WHO scale Grade 10) at Day 8, Day 15, Day 22, or Day 29 • Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifested by the requirement for and method of supplemental oxygen (WHO scale Grades 5-9) at Day 8, Day 15, Day 22, or • Day 29 • Severity of participant-reported symptoms of COVID-19-related illness using the Flu-PRO participant-reported outcome instrument (Days 1 to 15, Day 22 and Day 29) • Frequency of SARS-CoV-2 resistance mutations against VIR-7831 and VIR-7832, up to Day 29 • Host immune responses and exploratory biomarkers related to SARS-CoV-2, VIR-7831and/or VIR-7832, including genetic, cellular, transcriptomic, and proteomic parameters (including anti-SARS-CoV Nucleocapsid [N] antibody)

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Information regarding the Investigators who participated in this study and the associated ethics committees is provided in the List of Investigators and IECs/IRBs modular appendix. Information regarding study administrative structure is provided in the Study Administration Table modular appendix.

4. INVESTIGATIONAL PLAN

4.1. Study Design

This was a 3:1 randomized, blinded, placebo-controlled Phase 1 study of VIR-7832 versus placebo, followed by a 2:2:1 blinded, parallel group Phase 2a study of VIR-7832 versus VIR-7831 versus placebo. A Phase 1 was carried out to test the safety and tolerability of VIR-7832 in this group. Following review of safety and tolerability data from evaluated doses of VIR-7832, a dose (500 mg) was selected to progress to Phase 2a. The selected dose of VIR-7832 was further evaluated in a blinded, placebo -controlled randomized Phase 2a study, which planned to assess the safety and virological efficacy of VIR-7832 and VIR-7831.

4.2. Protocol Amendment(s)

The original protocol dated 18 January 2021 was amended 10 times (see Protocol and Protocol Amendments in the Modular Appendices).

4.3. Selection of Study Population

Adults (18 years to 65 years in Phase 1; ≥18 years in Phase 2a) with laboratory-confirmed SARS-CoV-2 infection (PCR).

Group B (mild-moderate disease) (WHO, 2020): Ambulant participants with peripheral capillary oxygen saturation (SpO2) and >94% Room Air (RA) and who have experienced symptoms of COVID-19 for ≤168 h (7 days).

Participants were required to 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, diarrhoea, shortness of breath on exertion, that began within 7 days of the planned dose of study drug. Within 7 days was defined as Day 0 being the symptom onset day and Day 7 being the last treatment day possible.

4.4. Treatments

4.4.1. Study Intervention(s) and Reference Therapy

Phase 1:

Single doses of VIR-7832 were administered by IV infusion over 1 hour. The starting dose was 50 mg, and dose escalations of 150 and 500 mg were performed, with escalation guided by emerging safety data and decision by the SRC. Duration of monitoring was 253 days post-dose (36 weeks) in line with the expected long half-life of VIR-7832.

Phase 2a:

A VIR-7832 dose of 500 mg was selected based on the safety and tolerability data from Phase 1. A 500 mg dose of VIR-7831 was also given by IV infusion over 1 hour, with matching placebo given by intravenous infusion over 1 hour in both parts of the study.

4.5. Study Assessments and Procedures

Study assessments and procedures are presented in Section 1.3 of the study protocol (Appendix 16.1.1).

4.5.1. Safety Assessments

The safety assessments were the monitoring of AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations.

The investigator or site staff were responsible for detecting, documenting and reporting events that met the definition of an AE or SAE. AE information volunteered by the participant, discovered by investigator questioning or detected by other means was collected from the start of study intervention until the follow-up contact.

The AE and SAE definitions are provided in the Protocol, Section 9.1. Laboratory and vital sign abnormalities are provided in the SAP Section 4.5.3.1.

4.5.2. Health Outcomes Assessments

Health outcomes assessments included severity of participant-reported symptoms of COVID-19-related illness using the Flu-PRO participant-reported outcome instrument (Days 1 to 15, Day 22 and Day 29).

4.5.3. Immunogenicity and Biomarkers Assessments

Immunogenicity and biomarker assessment included frequency of SARS-CoV-2 resistance mutations against VIR-7831 and VIR-7832, up to Day 29 and host immune responses and exploratory biomarkers related to SARS-CoV-2, VIR-7831 and/or VIR-7832, including genetic, cellular, transcriptomic, and proteomic parameters.

4.5.4. Clinical Assessment

Clinical assessments in Phase 2a included:

- Change from baseline to Day 8 in SARS-CoV-2 viral load
- Change from baseline over time, up to Day 29, in viral load
- Time to negative viral titres (Day 1-29)

- Proportion of participants with clinical improvement (as defined above) at day 8, 15 and day 29.
- Change at day 8 and 15 from randomization in the WHO Clinical Progression Scale.
- Time to a one point change on the WHO Clinical Progression Scale
- Change from baseline over time, up to Day 29, in SARS-CoV-2 specific T-cells frequencies in blood
- Proportion of participants who have progression of COVID-19 as defined by hospitalization (WHO scale Grade 4-9) >24 hrs or death (WHO scale Grade 10) at Day 8, Day 15, Day 22, or Day 29
- Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifested by the requirement for and method of supplemental oxygen (WHO scale Grades 5-9) at Day 8, Day 15, Day 22, or Day 29.

4.6. Data Quality Assurance

Participant data was entered remotely at sites to Medidata Rave EDC via tablet or other suitable access to the iMedidata SCTU URL and retained in accordance with the current Data Protection Regulations. The PI was responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

All participant data collected was pseudo anonymized, by assigning each participant a participant identifier code which was used to identify the participant during the study and for any participant specific clarification between SCTU and sites. The site retained a participant identification code list which is only available to site staff.

The Master Participant Information Sheet and Informed Consent Form outlined the participant data to be collected and how was to be managed or might be shared; including handling of all PID and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned were granted access to the eCRF. eCRF completion guidelines were provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorized by them were to enter or change data in the eCRFs. When requested, laboratory data was to be transcribed, with requested investigator observations entered into the eCRF. The original laboratory reports were to be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the study was available and a Study Schedule with planned and actual milestones, CRF tracking and central monitoring for active study management created.

Data queries were either automatically generated within the eCRF, or manually raised by the study team, if required. All alterations made to the eCRF were visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the study after all queries had been resolved and the database frozen, the PI confirmed the data integrity by electronically signing all the eCRFs. All data was downloaded and transferred to Sponsor for archiving. The eCRFs were archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

4.6.1. Quality Tolerance Limits

Not applicable.

4.6.2. Critical to Quality Factors

Not applicable.

4.7. Statistical Analyses

4.7.1. Sample Size Considerations

Phase 1:

The plan was to test 3 dose levels of VIR-7832 in 3 cohorts of 8 participants each (24 participants in total). Fewer than 3 cohorts and up to 32 participants (4 cohorts of 8 participants) could have been enrolled, with the final number dependent on dose escalation decisions. Each cohort included 6 VIR-7832 participants and 2 placebo.

Phase 2a:

A total of 125 additional participants were planned, randomized in a 2:2:1 ratio to VIR-7832, VIR-7831 and placebo. Participants who were randomized to placebo or the selected phase 2a dose of VIR-7832 in phase 1 were included in the analysis of phase 2a.

4.7.2. Analysis Sets

Please refer to Section 3 of the SAP for a description of analysis sets.

4.7.3. Interim Analyses

There were no interim analyses.

4.7.4. Final Analyses

Please refer to the GSK SAP and Output and Programming Specification (OPS) for a description of final analyses.

4.7.5. Changes in Conduct of the Study or Planned Analyses

It was agreed, prior to unblinding, that analyses of immunology endpoints will not be included in this CSR, and instead will be detailed in a separate report produced by Vir. This is a change from the planned analyses outlined in the GSK SAP. A summary of abnormal and clinically significant physical findings was not produced.

5. STUDY POPULATION RESULTS

5.1. Disposition of Participants

Most participants in each treatment group completed the study through Week 36 (Table 1). Reasons for withdrawal included lost to follow-up and withdrawal by participant. This study was stopped after the enrollment of 12 participants in Phase 2a.

Table 1 Summary of Participant Status and Participant Disposition for the Study Conclusion Record (ITT Population)

	Ph1 VIR-7832 (50mg) (N=6)	Ph1 VIR-7832 (150mg) (N=6)	Ph1 VIR-7832 (500mg) (N=6)	Ph2a VIR-7832 (500mg) (N=4)	Ph2a VIR-7831 (500mg) (N=6)	Ph1 Placebo (N=6)	Ph2a Placebo (N=2)
Participant Status							
COMPLETED [1]	4 (67%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)	2 (100%)
COMPLETED DAY 29	5 (83%)	6 (100%)	6 (100%)	4 (100%)	6 (100%)	6 (100%)	2 (100%)
WITHDRAWN	2 (33%)	0	0	0	0	0	0
Primary Reason [2] for Study Withdrawal							
LOST TO FOLLOW-UP	1 (17%)	0	0	0	0	0	0
WITHDRAWAL BY PARTICIPANT	1 (17%)	0	0	0	0	0	0

Source: Table 1.2
[1] A participant is considered to have completed the study if he/she has completed the study through Week 36.
[2] Participants may have only one primary reason
Abbreviations: Ph=Phase

5.2. Protocol Deviations

A summary of major protocol deviations is presented in Source Listing 2. Fifteen (15) of the 33 major protocol deviations were related to duration of infusion being outside of the protocol specified timeframe and had no impact on participant safety or study integrity.

5.3. Data Sets Analyzed

A summary of number of participants in each analysis set is presented in Table 2.

Table 2 Summary of Study Populations (Enrolled Population)

Population	Ph1 VIR-7832 (50mg) (N=6)	Ph1 VIR-7832 (150mg) (N=6)	Ph1 VIR-7832 (500mg) (N=6)	Ph2a VIR-7832 (500mg) (N=4)	Ph1/2a VIR-7832 (500mg) (N=10)	Ph2a VIR-7831 (500mg) (N=6)	Ph1 Placebo (N=6)	Ph2a Placebo (N=2)	Ph1/2a Placebo (N=8)
Enrolled	6 (100%)	6 (100%)	6 (100%)	4 (100%)	10 (100%)	6 (100%)	6 (100%)	2 (100%)	8 (100%)
Randomised	6 (100%)	6 (100%)	6 (100%)	4 (100%)	10 (100%)	6 (100%)	6 (100%)	2 (100%)	8 (100%)
Safety	6 (100%)	6 (100%)	6 (100%)	4 (100%)	10 (100%)	6 (100%)	6 (100%)	2 (100%)	8 (100%)
Intent-to-Treat (ITT)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	10 (100%)	6 (100%)	6 (100%)	2 (100%)	8 (100%)
Pharmacokinetic (PK)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	10 (100%)	6 (100%)	0	0	0
Virology	5 (83%)	6 (100%)	6 (100%)	4 (100%)	10 (100%)	6 (100%)	6 (100%)	2 (100%)	8 (100%)

Source: Table 1.1
Note: Analysis populations are defined in the Statistical Analysis Plan.
Abbreviations: Ph=Phase

5.4. Demographics and Baseline Characteristics

The majority of participants were white (Table 3). The age ranged from 19 to 72 years (median range: 23.5 to 53.0) (Source Table 1.4). The majority of participants in each treatment group exhibited COVID-19 symptoms of cough and malaise. The mean time from symptom onset to first dose of treatment ranged from 3.8 to 5.8 days among the treatment groups and 4.0 to 4.2 days for the placebo groups.

Table 3 Summary of Demographic and Baseline Characteristics (ITT Population)

	Ph1 VIR-7832 (50mg) (N=6)	Ph1 VIR-7832 (150mg) (N=6)	Ph1 VIR-7832 (500mg) (N=6)	Ph2a VIR-7832 (500mg) (N=4)	Ph1/2a VIR-7832 (500mg) (N=10)	Ph2a VIR-7831 (500mg) (N=6)	Ph1 Placebo (N=6)	Ph2a Placebo (N=2)	Ph1/2a Placebo (N=8)	Ph1 Total (N=24)	Ph2a Total (N=12)	Ph1/2a Total (N=36)
Sex												
N	6	6	6	4	10	6	6	2	8	24	12	36
Male	5 (83%)	4 (67%)	4 (67%)	1 (25%)	5 (50%)	1 (17%)	3 (50%)	1 (50%)	4 (50%)	16 (67%)	3 (25%)	19 (53%)
Female	1 (17%)	2 (33%)	2 (33%)	3 (75%)	5 (50%)	5 (83%)	3 (50%)	1 (50%)	4 (50%)	8 (33%)	9 (75%)	17 (47%)
Age (YEARS)[1]												
N	6	6	6	4	10	6	6	2	8	24	12	36
Mean	26.5	25.3	24.2	44.3	32.2	52.8	28.5	46.0	32.9	26.1	48.8	33.7
SD	6.57	5.82	4.22	16.68	14.50	17.30	12.44	16.97	14.74	7.54	16.00	15.35
High Level Race												
N	6	6	6	4	10	6	6	2	8	24	12	36
WHITE	6 (100%)	6 (100%)	5 (83%)	4 (100%)	9 (90%)	6 (100%)	4 (67%)	2 (100%)	6 (75%)	21 (88%)	12 (100%)	33 (92%)
MIXED RACE	0	0	1 (17%)	0	1 (10%)	0	2 (33%)	0	2 (25%)	3 (13%)	0	3 (8%)
BMI (kg/m^2)[2]												
N	6	6	6	4	10	6	6	2	8	24	12	36
Mean	22.23	24.02	24.13	32.28	27.39	35.02	24.68	28.60	25.66	23.77	33.03	26.86
SD	5.250	6.329	3.222	8.365	6.839	7.569	3.380	10.182	5.124	4.509	7.777	7.211
Baseline WHO Clinical Progression Score (continuous)												
N	6	6	6	4	10	6	6	2	8	24	12	36
Mean	2.0	1.8	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
SD	0.00	0.41	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.00	0.17
Time from symptom onset to first dose (days)												

	Ph1 VIR-7832 (50mg) (N=6)	Ph1 VIR-7832 (150mg) (N=6)	Ph1 VIR-7832 (500mg) (N=6)	Ph2a VIR-7832 (500mg) (N=4)	Ph1/2a VIR-7832 (500mg) (N=10)	Ph2a VIR-7831 (500mg) (N=6)	Ph1 Placebo (N=6)	Ph2a Placebo (N=2)	Ph1/2a Placebo (N=8)	Ph1 Total (N=24)	Ph2a Total (N=12)	Ph1/2a Total (N=36)
N	6	6	6	4	10	6	6	2	8	24	12	36
Mean	5.8	3.8	4.3	4.3	4.3	5.0	4.2	4.0	4.1	4.5	4.6	4.6
SD	0.98	1.94	1.63	0.96	1.34	1.26	1.60	1.41	1.46	1.67	1.16	1.50

Source: Table 1.4
[1] Age at consent, collected at site.
[2] BMI, collected at site.
Note: Percentages are calculated from the displayed n counts.
Note: WHO scores are measured from 0 to 10 with 0 being the least severe and 10 being the most severe score.
Abbreviations: Max = maximum; Min = minimum; Ph=Phase; Q = quartile

5.5. Exposure

All participants received the full dose of infusion (Source Table 1.5). Infusion was interrupted for 8 participants in the treatment groups and 2 participants in the placebo groups. Most interruptions were brief and due to cannular obstructions (Source Listing 5).

6. SAFETY RESULTS

6.1. Adverse Events

A total of 21, 6, and 8 participants who received VIR-7832, VIR-7831, and placebo, respectively, reported AEs (nonserious AEs and SAEs) (Table 4). Of these, 4 participants who received VIR-7832 and 1 participant who received placebo reported non-serious events that were considered related to study treatment (Source Listing 6). None of these events were reported more than once for each group. Two participants who received VIR-7832 and 1 participant who received VIR-7831 reported SAEs, none of which were fatal or related to study treatment (Source Listing 7 and Table 7). There were no AEs leading to permanent discontinuation of study treatment or dose interruption/delay.

Table 4 Overall Summary of Adverse Events (Safety Population)

	Ph1 VIR-7832 (50mg) (N=6)	Ph1 VIR-7832 (150mg) (N=6)	Ph1 VIR-7832 (500mg) (N=6)	Ph2a VIR-7832 (500mg) (N=4)	Ph2a VIR-7831 (500mg) (N=6)	Ph1 Placebo (N=6)	Ph2a Placebo (N=2)
Any AE	6 (100%)	6 (100%)	5 (83%)	4 (100%)	6 (100%)	6 (100%)	2 (100%)
Non-Serious AEs related to study treatment	1 (17%)	2 (33%)	1 (17%)	0	0	1 (17%)	0
AEs leading to permanent discontinuation of study treatment	0	0	0	0	0	0	0
AEs leading to dose interruption/delay	0	0	0	0	0	0	0
Any SAE	1 (17%)	0	0	1 (25%)	1 (17%)	0	0
SAEs related to study treatment	0	0	0	0	0	0	0
Fatal SAEs	0	0	0	0	0	0	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0

Source: Table 3.1
Abbreviations: AE = adverse event; N = number of participants; Ph=Phase; SAE = serious adverse event

6.1.1. Common Adverse Events

A summary by PT and SOC is presented for all AEs (nonserious AEs and SAEs) in Source Table 3.2 and for all SAEs in Source Table 3.3. AEs occurring in >2 participants each in any dose group are reported in Table 5, among which headache was the most common AE. The most common AEs by treatment were headache for participants who received VIR-7832 or VIR-7831, and COVID-19 for participants who received placebo.

Table 5 Summary of Common (>2 Participants per Preferred Term in Any Dose Group) Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Ph1 VIR-7832 (50mg) (N=6)	Ph1 VIR-7832 (150mg) (N=6)	Ph1 VIR-7832 (500mg) (N=6)	Ph2a VIR-7832 (500mg) (N=4)	Ph2a VIR-7831 (500mg) (N=6)	Ph1 Placebo (N=6)	Ph2a Placebo (N=2)
ANY EVENT	6 (100%)	6 (100%)	5 (83%)	4 (100%)	6 (100%)	6 (100%)	2 (100%)
Respiratory, thoracic and mediastinal disorders	5 (83%)	2 (33%)	3 (50%)	3 (75%)	5 (83%)	4 (67%)	1 (50%)
Nasal congestion	3 (50%)	1 (17%)	0	0	0	1 (17%)	1 (50%)
Cough	1 (17%)	1 (17%)	2 (33%)	2 (50%)	0	1 (17%)	0
Eye disorders	3 (50%)	1 (17%)	0	0	2 (33%)	1 (17%)	0
Photophobia	3 (50%)	0	0	0	0	0	0
Nervous system disorders	4 (67%)	4 (67%)	3 (50%)	1 (25%)	3 (50%)	2 (33%)	0
Headache	3 (50%)	3 (50%)	2 (33%)	0	3 (50%)	1 (17%)	0
Infections and infestations	2 (33%)	2 (33%)	2 (33%)	3 (75%)	3 (50%)	4 (67%)	0
COVID-19	1 (17%)	2 (33%)	0	0	0	3 (50%)	0

Source: Table 3.2
Abbreviations: Ph=Phase

6.1.2. Treatment-related Adverse Events

AEs considered by the investigators as related to study treatment occurred in 4 participants (Source Table 3.1) and included 1 event of nausea and 1 event of Fibrin D dimer increased in 1 participant in the Ph1 VIR-7832 (50 mg) treatment group, 2 events of Grade 2 neutrophil count decreased in 1 participant in the Ph1 VIR-7832 (500 mg) treatment group, and 2 skin rashes reported by 2 participants receiving 150 mg VIR-7832. As detailed in the brief narratives, further dermatology investigation, including biopsies, were performed:

- Thirty seven-year-old white female with a medical history of hypothyroidism on treatment with levothyroxine. A generalized pruritic rash under breast and on torso and arms was reported on Day 58 post dose and treated with miconazole. After biopsy reported diagnosis was lichenoid keratosis and there were no associated AEs (Source Table 1.6, Listings 6 and 10).
- Twenty one-year-old white male with no relevant medical history or concomitant medications, complained of pruritus on day 77 and subsequently, on day 144 post dose and reported a pruritic rash. After biopsy, the investigator documented the skin reaction as a maculopapular rash. There were no associated AEs in this participant (Source Table 1.6, Listings 6 and 10).

There also was an event of Grade 3 neutrophil count decreased in 1 participant in the Ph1 Placebo treatment group which was classified as treatment-related by the investigator (Source Listing 6).

6.1.3. Adverse Events by Grade

A summary by PT, SOC, and grade is presented for all AEs in Source Table 3.2. AEs are presented by grade in Source Table 3.2. There were 12 Grade 3 - AEs reported: (Table 6). All SAEs were Grade 2 or Grade 3 in severity (Section 6.2.2). There were no Grade 4 or Grade 5 AEs reported (Source Listing 6 and Source Listing 7).

Table 6 Listing of All ≥ Grade 3 Adverse Events (Safety Population)

Treatment/ Participant ID	Age (years)/ Sex	SOC/PT	Outcome/ Onset Date/ Date of Resolution/ Duration (Days)	Time Since Dose (Days)	Maximum Grade	Action taken/Relation to study treatment
Ph1 VIR-7832 (150mg)/ V1-1001005	24/F	Nervous system disorders/ Syncope	Recovered/resolved/ 2021-07-21/ 2021-07-21/ 1d	1	3	Dose not changed/ Not related
Ph2a VIR-7831 (500mg)/ V2-1001001	51/F	Cardiac disorders/ Acute myocardial infarction[a]	Recovered/resolved/ 2022-05-02/ 2022-09-15/ 137d	8	3	Dose not changed/ Not related
		Cardiac disorders/ Coronary artery disease	Recovering/resolving/ 2022-05-02/	8	3	Dose not changed/ Not related
		Surgical and medical procedures/ Coronary artery bypass[a]	Recovered/resolved with sequalae/ 2022-05-31/ 2022-05-31/ 1d	37	3	Dose not changed/ Not related
		Renal and urinary disorders/ Acute kidney injury[a]	Recovered/resolved/ 2022-06-01/ 2022-06-19/ 19d	38	3	Dose not changed/ Not related
		Respiratory, thoracic and mediastinal disorders/ Pleural effusion[a]	Recovered/resolved/ 2022-06-01/ 2022-06-23/ 23d	38	3	Dose not changed/ Not related
		Eye disorders/ Vitreous floaters	Recovering/resolving/ 2022-09-08/	137	3	Dose not changed/ Not related
		Infections and infestations/ Wound infection[a]	Recovered/resolved/ 2022-12-03/ 2022-12-14/ 12d	223	3	Dose not changed/ Not related
Ph2a VIR-7832 (500mg)/ V2-1049007	47/M	Infections and infestations/ Bacteraemia[a]	Recovered/resolved/ 2022-09-09/ 2022-09-20/ 12d	149	3	Dose not changed/ Not related
Ph1 Placebo/ V1-1049006	23/M	Gastrointestinal disorders/ Diarrhoea	Recovered/resolved/ 2021-08-06/ 2021-08-13/ 8d	59	3	Dose not changed/ Not related
Ph1 Placebo/ V1-1049007	20/M	Investigations/ Neutrophil count decreased	Recovered/resolved/ 2021-07-30/ 2021-08-19/ 21d	31	3	Dose not changed/ Not related

Source: Listing 6
Abbreviations: d=days; F=female; ID=identifier; M=male; Ph=Phase; PT=preferred term; SAE = serious adverse event; SOC=system organ class

a. Reported as an SAE

6.2. Serious and Other Significant Adverse Events

6.2.1. Deaths

No deaths were reported in this study (Source Table 3.1, Source Listing 6, and Source Listing 7).

6.2.2. Other Serious Adverse Events

Three participants reported SAEs, none of which were fatal or related to study treatment (Table 7).

Table 7 Listing of All Serious Adverse Events (Safety Population)

Treatment/ Participant ID	Age (years)/ Sex	SOC/PT	Outcome/ Onset Date/ Date of Resolution/ Duration (Days)	Time Since Dose (Days)	Maximum Grade	Action taken/Relation to study treatment
Ph2a VIR-7831 (500mg)/ V2-1001001	51/F	Cardiac disorders/ Acute myocardial infarction	Recovered/resolved with sequelae/ 2022-05-02/ 2022-06-23/ 53d	8	3	Dose not changed/ Not related
		Surgical and medical procedures/ Coronary artery bypass	Recovered/resolved/ 2022-05-31/ 2022-05-31/ 1d	37	3	Dose not changed/ Not related
		Renal and urinary disorders/ Acute kidney injury	Recovered/resolved/ 2022-06-01/ 2022-06-19/ 19d	38	3	Dose not changed/ Not related
		Respiratory, thoracic and mediastinal disorders/ Pleural effusion	Recovered/resolved/ 2022-06-01/ 2022-06-23/ 23d	38	3	Dose not changed/ Not related
		Infections and infestations/ Wound infection	Recovered/resolved/ 2022-12-03/ 2022-12-14/ 12d	223	3	Dose not changed/ Not related
Phl VIR-7832 (50mg)/ Vl-1049002	28/M	Respiratory, thoracic and mediastinal disorders/ Respiratory disorder (Dyspnoea)	Recovered/resolved/ 2021-06-11/ 2021-06-12/ 2d	9	2	Dose not changed/ Not related

Treatment/ Participant ID	Age (years)/ Sex	SOC/PT	Outcome/ Onset Date/ Date of Resolution/ Duration (Days)	Time Since Dose (Days)	Maximum Grade	Action taken/Relation to study treatment
Ph2a VIR-7832 (500mg)/ V2-1049007	47/M	Infections and infestations/ Staphylococcal bacteraemia	Recovered/resolved/ 2022-09-09/ 2022-09-20/ 12d	149	3	Dose not changed/ Not related

Source: Listing 7
Abbreviations: d=days; F=female; ID=identifier; M=male; Ph=Phase; PT=preferred term; SOC=system organ class

6.2.3. Other Significant Adverse Events

No other significant AEs were reported in this study (Source Table 3.1, Source Listing 6, and Source Listing 7).

6.3. Clinical Laboratory Evaluations

Changes in laboratory parameters were consistent with baseline conditions and underlying COVID-19 disease (Source Table 3.5, Source Table 3.6, and Source Listing 9). Based on review of clinical laboratory results, there were no trends or patterns noted and no new safety issues were identified.

6.4. Vital Signs

Changes in vital signs were consistent with baseline conditions and underlying COVID-19 disease (Source Table 3.4). Based on review of vital signs results, no new safety issues were identified.

6.5. Dose-Limiting Toxicity

One participant in the Ph1 VIR-7832 (150 mg) treatment group experienced a DLT of Grade 3 syncope 1 day after dosing that lasted 1 day and was judged not related to study treatment by the investigator (Source Listing 8).

6.6. Pregnancies

There were no pregnancies reported in the study.

7. CLINICAL ENDPOINT RESULTS

7.1. Pharmacokinetics

This report presents final VIR-7832 and VIR-7831 PK results from Phase 1 and Phase 2a through Week 24. Serum VIR-7832 PK data from Phase 1 are available from 3 cohorts of 50 mg, 150 mg, and 500 mg IV VIR-7832 from 6 participants in each cohort. Serum VIR-7832 and VIR-7831 PK data from Phase 2a are available from 4 participants who received 500 mg IV VIR-7832 and 6 participants who received 500 mg IV VIR-7831. Noncompartmental analysis (NCA) was performed and the derived PK parameters for VIR-7832 and VIR-7831 are summarized in Table 8. PK profiles for VIR-7832 50 mg, 150 mg, and 500 mg and VIR-7831 500 mg are presented in Figure 1 to Figure 4, respectively.

Table 8 Summary of Derived VIR-7832 Serum Pharmacokinetic Parameters by Treatment: Phase 1 and 2a

Parameter	Ph 1 VIR-7832 (50 mg) (N=6)[a]	Ph 1 VIR-7832 (150 mg) (N=6)[b]	Ph 1 VIR-7832 (500 mg) (N=6)[c]	Ph 2a VIR-7832 (500 mg) (N=4)	Ph I/2a VIR-7832 (500 mg) (N=10)[d]	Ph 2a VIR-7831 (500 mg) (N=6)[e]
C_{max}, µg/mL	16.8 (15.56)	52.9 (13.74)	174.8 (9.02)	177.8 (11.92)	176.1 (9.73)	182.7 (12.65)
C_{last}, µg/mL	0.7 (166.28)	2.5 (29.14)	6.5 (51.23)	5.8 (14.07)	6.2 (38.71)	7.0 (170.72)
C_{Day29}, µg/mL	4.58 (3.67)	14.16 (21.62)	47.19 (19.31)	36.21 (17.46)	42.45 (22.43)	44.08 (50.24)
T_{max}, day	0.084 (0.05, 0.30)	0.105 (0.05, 0.13)	0.045 (0.04, 0.13)	0.046 (0.04, 0.05)	0.046 (0.04, 0.13)	0.050 (0.04, 0.06)
T_{last}, day	168 (6.80, 175)	168 (154, 196)	168 (145, 182)	168 (160, 169)	168 (145, 182)	168 (167, 175)
AUC_{D1-29}, day*µg/mL	189.9 (6.22)	593.4 (13.78)	1908.2 (13.48)	1976.8 (7.09)	1935.3 (10.99)	1948.3 (23.67)
AUC_{0-last}, day*µg/mL	326.5 (90.93)	1552.2 (18.55)	4651.1 (13.92)	4477.3 (8.29)	4580.8 (11.58)	4874.4 (45.18)
$\%AUC_{exp}$	5.8 (12.48)	9.7 (22.69)	7.5 (15.48)	8.5 (26.96)	7.9 (20.94)	9.0 (150.44)
AUC_{inf}, day*µg/mL	475.5 (7.87)	1811.2 (16.80)	4792 (6.90)	4908.5 (7.54)	4843.4 (6.83)	5525.7 (59.49)
CL, mL/day	105.2 (7.87)	82.8 (16.80)	104.3 (6.90)	101.9 (7.54)	103.2 (6.83)	90.5 (59.49)
V_z, L	6.32 (5.59)	6.09 (17.64)	7.02 (10.78)	7.39 (16.04)	7.18 (12.73)	7.16 (24.18)
V_{ss}, L	6.04 (4.92)	5.85 (15.13)	6.65 (9.60)	6.55 (10.53)	6.61 (9.40)	6.39 (16.75)
$t_{1/2}$, day	40.7 (39.1, 46.9)	48.5 (45.1, 60.7)	47.4 (43.3, 49.8)	49.9 (42.8, 60.0)	48.2 (42.8, 60.0)	61.5 (29.4, 75.7)

Source: Table 4.2, Table 4.3, and Table 4.4.

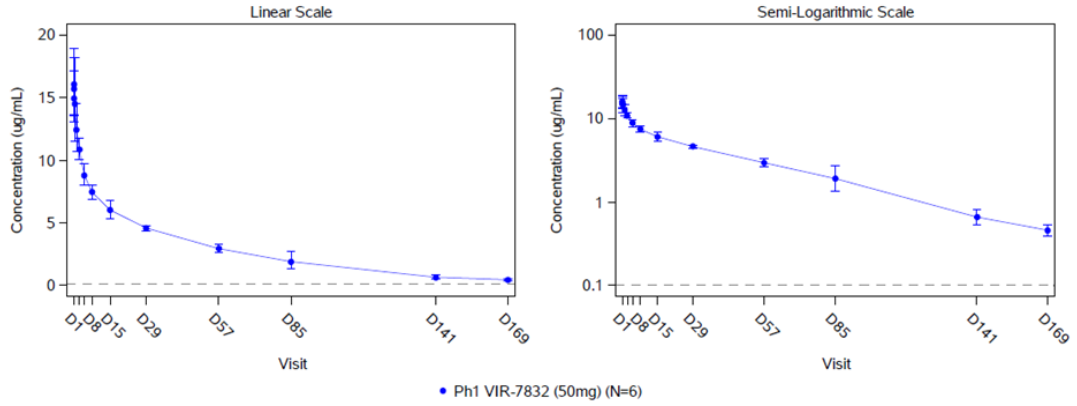
Parameters are reported as geometric mean ($\%CV_b$) except for T_{max}, T_{last} and $t_{1/2}$, which are presented as median (min, max).

[a] N=5 for C_{Day29}, AUC_{D1-29} and AUC_{inf} and all related parameters as 1 participant had no data past Study Day 8 ($\%AUC_{exp}$ <20%).

[b] N=5 for AUC_{inf} and all related parameters as 1 participant had $\%AUC_{exp}$ <20%.

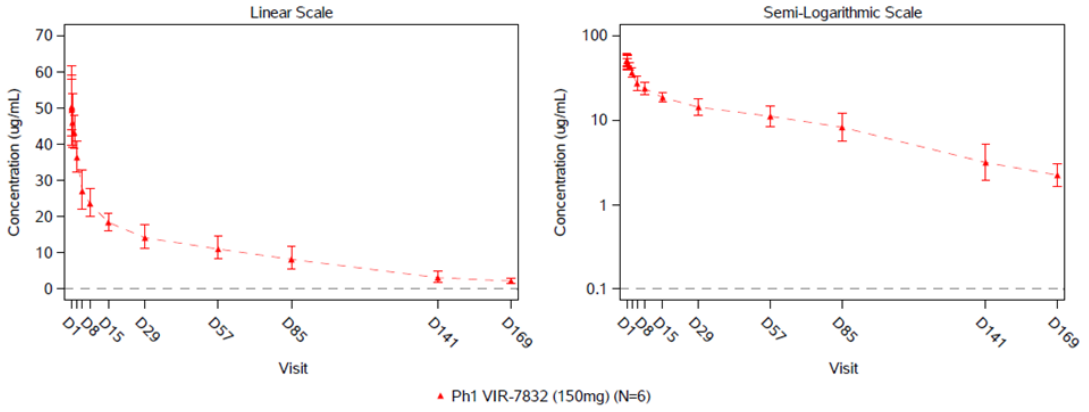
[c] N=5 for C_{max} and T_{max} as 1 participant had no EOI concentration data, and N=5 for AUC_{inf} and all related parameters as 1 participant had $\%AUC_{exp}$ <20%.
[d] N=9 for C_{max} and T_{max} as 1 participant in Phase 1 had no EOI concentration data, and N=9 for AUC_{inf} and all related parameters as 1 participant in Phase 1 had $\%AUC_{exp}$ <20%.
[e] N=5 for C_{max} and T_{max} as 1 participant had no EOI concentration data, and N=5 for AUC_{inf} and all related parameters as 1 participant had $\%AUC_{exp}$ <20%.
Note: Where PK actual sample time was not recorded, time has been imputed for the NCA analysis as follows: Start of infusion – 1 h for pre-dose; End of infusion (EOI) + 24 h for EOI + 24 h; 12 pm for Day 3 onwards.

Figure 1 Geometric Mean (95% CI) VIR-7832 50 mg Serum Concentration - Time Plots (Linear and Semi-log)



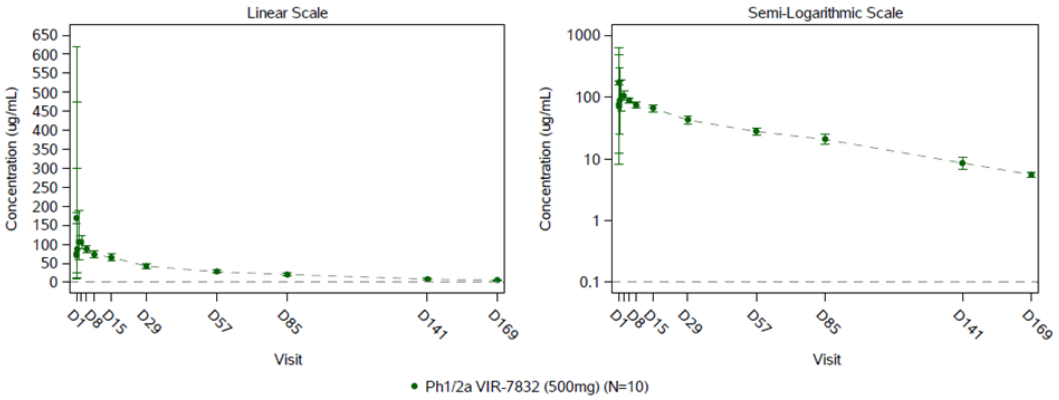
Source: Figure 4.5
Note: LLQ=0.1 µg/mL
Note: Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist and measurable concentrations after >1 consecutive mid-profile non-quantifiable result.

Figure 2 Geometric Mean (95% CI) VIR-7832 150 mg Serum Concentration - Time Plots (Linear and Semi-log)



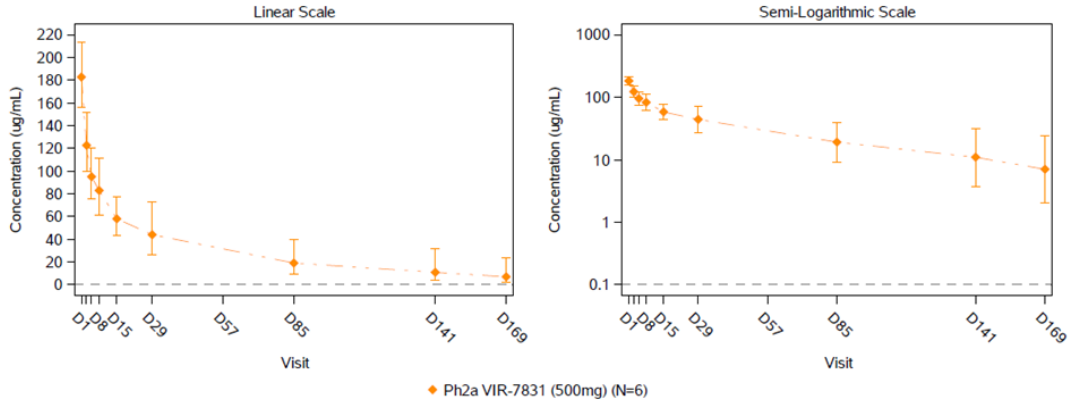
Source: Figure 4.5
Note: LLQ=0.1 µg/mL
Note: Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist and measurable concentrations after >1 consecutive mid-profile non-quantifiable result.

Figure 3 Geometric Mean (95% CI) VIR-7832 500 mg Serum Concentration - Time Plots (Linear and Semi-log)



Source: Figure 4.5
Note: LLQ=0.1 µg/mL
Note: Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist and measurable concentrations after >1 consecutive mid-profile non-quantifiable result.
Note: VIR-7832 500 mg dose includes all participants (Ph 1 and Ph 2a) receiving this dose.
Note: Ph 1 PK samples are collected at Day 1 (Pre-dose, EOI, EOI + 1hr, EOI + 2hr, EOI + 6hr, EOI + 24hr) and Days 3, 5, 8, 15, 29, 57, 85, 141 and 169. Ph 2a PK samples are collected at Day 1 (Pre-dose, EOI) and Days 3, 5, 8, 15, 29, 85, 141 and 169.

Figure 4 Geometric Mean (95% CI) VIR-7831 500 mg Serum Concentration - Time Plots (Linear and Semi-log)



Source: Figure 4.6
Note: LLQ=0.1 µg/mL
Note: Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist and measurable concentrations after >1 consecutive mid-profile non-quantifiable result.

7.2. Immunogenicity

A validated, multi-tiered approach to evaluate anti-VIR-7831 and anti-VIR-7832 antibodies, consisting of screening, confirmation, and titration assays was implemented.

Titer, in this study, is defined as the reciprocal of the highest dilution of the sample (including minimum required dilution) that yields a positive result.

ADA were detected in one out of six participants in 50 mg VIR-7832 dose group and 1 out of 6 participants in 150 mg dose group of VIR-7832 in phase 1 cohort (Source Table 5.2). Transient treatment-emergent ADA was detected in 1 of 6 participants in 150 mg dose group with titer value 40. The persistent treatment emergent ADA was observed in 1 of 6 participants from VIR-7832 (50 mg) with titer range of 80 to 320 (Source Table 5.3). There was no apparent impact of ADA on VIR-7831/VIR7832 exposure or safety.

7.3. Virology

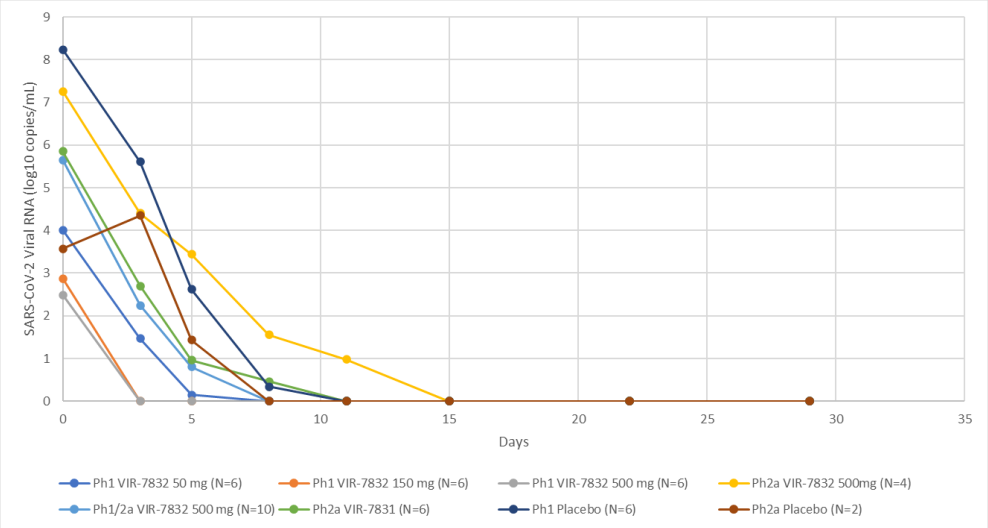
There was no formal analysis planned for the SARS-CoV-2 viral RNA quantitation data in Phase 1 of the study. Formal assessment of the SARS-CoV-2 viral RNA quantitation data was planned for Phase 2 of the study; this was not completed due to the discontinuation of Phase 2 of the study leading to smaller than planned sample size (n=12/125).

7.3.1. Kinetics of SARS-CoV-2 Viral RNA

The level of SARS-CoV-2 RNA in participants in Phase 1 and Phase 2a of AGILE was measured by qRT-PCR. In Phase 1, participants receiving 50, 150 or 150 mg VIR-7832 (N=6 at each dose) had median baseline viral loads ranging from 2.491 to 4.012 $\log_{10}$ copies/mL and a median change in viral load ranging from -2.491 to -3.889 $\log_{10}$ copies/mL observed at Day 29 (Table 9, Table 10, Figure 5). Participants receiving placebo (N=6) in Phase 1 had a median baseline viral load of 8.237 $\log_{10}$ copies/mL and a median change in viral load of -8.237 $\log_{10}$ copies/mL observed at Day 29.

In Phase 2a, participants receiving 500 mg VIR-7832 (N=4) had a median baseline viral load of 7.257 $\log_{10}$ copies/mL and median change from baseline viral load-7.257 $\log_{10}$ copies/mL at Day 29 (Table 9, Table 10, Figure 5). Participants receiving placebo (N=2) and VIR-7831 (N=6) in Phase 2a had a median baseline viral load of 3.573 $\log_{10}$ copies/mL and 5.857 $\log_{10}$ copies/mL, respectively, and a median change in viral load of -3.573 $\log_{10}$ copies/mL and -5.816 $\log_{10}$ copies/mL observed at Day 29, respectively (Table 9, Table 10, Figure 5).

Figure 5 Median SARS-CoV-2 Viral RNA Kinetics



Source: Table 2.2.
Note: Baseline value is defined as the latest non-missing pre-dose assessment, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose.
Note: Negative viral load results have been imputed as zero to align with the approach of the sponsor.

Table 9 Summary of Absolute Viral Load (log_{10} copies/mL) Through Day 29 as Measured by qRT-PCR

Visit	Change from Baseline Viral Load (log_{10} copies/mL)	Phase 1				Phase 2a			Phase 1 + Phase 2a	
		Placebo (N=6)	VIR-7832 50 mg (N=6)	VIR-7832 150 mg (N=6)	VIR-7832 500 mg (N=6)	Placebo (N=2)	VIR-7832 500 mg (N=4)	VIR-7831 500 mg (N=6)	Placebo (N=8)	VIR-7832 500 mg (N=10)
Baseline	N	6	5	6	6	2	4	6	8	10
	Mean (SD)	7.608 (3.1806)	4.227 (1.4785)	3.374 (2.9000)	3.180 (3.5530)	3.573 (1.2560)	7.224 (0.9501)	6.426 (2.0355)	6.599 (3.3077)	4.798 (3.4171)
	Median (Min, Max)	8.237 (2.16, 11.55)	4.012 (2.58, 6.63)	2.873 (0, 8.75)	2.491 (0, 8.92)	3.573 (2.68, 4.46)	7.257 (6.13, 8.25)	5.857 (4.50, 9.91)	7.188 (2.16. 11.55)	5.654 (0, 8.92)
Day 3	N	6	6	6	6	2	4	5	8	10
	Mean (SD)	4.500 (2.8079)	1.602 (1.5070)	0.466 (1.0016)	0.748 (1.1599)	4.351 (1.0001)	4.450 (0.4273)	2.475 (0.6561)	4.463 (2.4040)	2.229 (2.1127)
	Median (Min, Max)	5.611 (0.42, 6.91)	1.467 (0, 3.52)	0 (0, 2.5)	0 (0, 2.32)	4.351 (3.64, 5.06)	4.399 (3.99, 5.01)	2.701 (1.75, 3.09)	5.264 (0.42, 6.91)	2.244 (0, 5.01)
Day 5	N	6	6	6	6	2	4	6	8	10
	Mean (SD)	2.827 (2.0677)	0.361 (0.4764)	0.140 (0.3424)	0.404 (0.6633)	1.432 (0.9436)	3.588 (3.1197)	1.923 (2.3641)	2.478 (1.8969)	1.678 (2.4883)
	Median (Min, Max)	2.620 (0, 6)	0.147 (0, 1.13)	0 (0, 0.84)	0 (0, 1.56)	1.432 (0.76, 2.1)	3.439 (0.74, 6.74)	0.957 (0, 5.44)	2.042 (0, 6)	0.801 (0, 6.74)
Day 8	N	6	4	6	6	2	4	5	8	10
	Mean (SD)	1.154 (1.9231)	0 (0)	0 (0)	0 (0)	0 (0)	1.979 (2.3902)	0.864 (1.0517)	0.865 (1.7109)	0.792 (1.7173)
	Median (Min, Max)	0.338 (0, 4.95)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	1.551 (0, 4.82)	0.463 (0, 2.43)	0.084 (0, 4.95)	0 (0, 4.82)
Day 11	N	6	6	6	6	2	4	6	8	10
	Mean (SD)	0.669 (1.0665)	0.866 (1.746)	0 (0)	0 (0)	0 (0)	1.085 (1.2650)	0 (0)	0.502 (0.9531)	0.434 (0.9206)
	Median (Min, Max)	0 (0, 2.40)	0 (0, 4.36)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.98 (0, 2.38)	0 (0, 0)	0 (0, 2.4)	0 (0, 2.38)
Day 15	N	6	5	6	6	2	4	6	8	10
	Mean (SD)	0.069 (0.1688)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.052 (0.1462)	0 (0)
	Median (Min, Max)	0 (0, 0.41)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0.41)	0 (0, 0)
Day 22	N	6	5	6	6	2	4	6	8	10
	Mean (SD)	0 (0)	0.12 (0.2691)	0 (0)	0 (0)	0 (0)	0.635 (1.2699)	0 (0)	0 (0)	0.254 (0.8032)
	Median (Min, Max)	0 (0, 0)	0 (0, 0.60)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 2.54)	0 (0, 0)	0 (0, 0)	0 (0, 2.54)
Day 29	N	6	5	6	6	2	4	6	8	10

Visit	Change from Baseline Viral Load (log_{10} copies/mL)	Phase 1				Phase 2a			Phase 1 + Phase 2a	
		Placebo (N=6)	VIR-7832 50 mg (N=6)	VIR-7832 150 mg (N=6)	VIR-7832 500 mg (N=6)	Placebo (N=2)	VIR-7832 500 mg (N=4)	VIR-7831 500 mg (N=6)	Placebo (N=8)	VIR-7832 500 mg (N=10)
	Mean (SD)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.933 (1.4506)	0 (0)	0 (0)
	Median (Min, Max)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 3.00)	0 (0, 0)	0 (0, 0)

Source: Table 2.3. Baseline value is defined as the latest non-missing pre-dose assessment, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose. Negative viral load results have been imputed as zero to align with the approach of the sponsor.

Table 10 Summary of Change from Baseline in Viral Load (log_{10} copies/mL) Through Day 29 as Measured by qRT-PCR

Visit	Change from Baseline Viral Load (log_{10} copies/mL)	Phase 1				Phase 2a			Phase 1 + Phase 2a	
		Placebo (N=6)	VIR-7832 50 mg (N=6)	VIR-7832 150 mg (N=6)	VIR-7832 500 mg (N=6)	Placebo (N=2)	VIR-7832 500 mg (N=4)	VIR-7831 500 mg (N=6)	Placebo (N=8)	VIR-7832 500 mg (N=10)
Day 3	N	6	5	6	6	2	4	5	8	10
	Mean (SD)	-3.108 (1.8753)	-2.937 (2.7197)	-2.908 (2.0345)	-2.432 (2.8575)	0.778 (0.2559)	-2.774 (1.3266)	-3.909 (1.7978)	-2.136 (2.3996)	-2.569 (2.2703)
	Median (Min, Max)	-2.455 (-6.08, -1.23)	-2.753 (-6.63, 0.94)	-2.750 (-6.26, 0)	-1.330 (-6.76, 0)	0.778 (0.60, 0.96)	-2.858 (-4.26, -1.12)	-3.247 (-6.82, -2.38)	-2.038 (-6.08, 0.96)	-2.103 (-6.76, 0.00)
Day 5	N	6	5	6	6	2	4	6	8	10
	Mean (SD)	-4.781 (1.5460)	-3.942 (1.4815)	-3.234 (2.9790)	-2.776 (3.6459)	-2.141 (0.3124)	-3.636 (3.1398)	-4.503 (3.3247)	-4.121 (1.7930)	-3.120 (3.2967)
	Median (Min, Max)	-4.958 (-6.39, -2.16)	-3.767 (-6.34, -2.58)	-2.873 (-8.75, 0)	-1.279 (-8.92, 0)	-2.141 (-2.36, -1.92)	-3.200 (-7.17, -0.98)	-3.838 (-9.82, -0.93)	-4.302 (-6.39, -1.92)	-1.757 (-8.92, 0)
Day 8	N	6	4	6	6	2	4	5	8	10
	Mean (SD)	-6.454 (3.7348)	-4.281 (1.7016)	-3.374 (2.9000)	-3.180 (3.5530)	-3.573 (1.2560)	-5.245 (2.4276)	-5.521 (2.2605)	-5.734 (3.4595)	-4.006 (3.1804)
	Median (Min, Max)	-6.540 (-11.38, -1.65)	-3.955 (-6.63, -2.58)	-2.873 (-8.75, 0)	-2.491 (-8.92, 0)	-3.573 (-4.46, -2.68)	-4.903 (-8.25, -2.92)	-4.998 (-9.44, -3.66)	-4.696 (-11.38, -1.65)	-3.871 (-8.92, 0)
Day 11	N	6	5	6	6	2	4	6	8	10
	Mean (SD)	-6.939 (3.3841)	-3.188 (3.0740)	-3.374 (2.9000)	-3.180 (3.5530)	-3.573 (1.2560)	-6.139 (1.5950)	-6.426 (2.0355)	-6.097 (3.2915)	-4.363 (3.1932)
	Median (Min, Max)	-7.035 (-11.55, -2.16)	-3.767 (-6.63, 1.78)	-2.873 (-8.75, 0)	-2.491 (-8.92, 0)	-3.573 (-4.46, -2.68)	-5.956 (-8.25, -4.39)	-5.857 (-9.91, -4.50)	-5.270 (-11.55, -2.16)	-4.784 (-8.92, 0)
Day 15	N	6	4	6	6	2	4	6	8	10
	Mean (SD)	-7.539 (3.2207)	-3.626 (0.7129)	-3.374 (2.9000)	-3.180 (3.5530)	-3.573 (1.2560)	-7.224 (0.9501)	-6.426 (2.0355)	-6.547 (3.3175)	-4.798 (3.4171)
	Median (Min, Max)	-8.237 (-11.55, -2.16)	-3.889 (-4.14, -2.58)	-2.873 (-8.75, 0)	-2.491 (-8.92, 0)	-3.573 (-4.46, -2.68)	-7.257 (-8.25, -6.13)	-5.857 (-9.91, -4.50)	-6.981 (-11.55, -2.16)	-5.654 (-8.92, 0)
Day 22	N	6	4	6	6	2	4	6	8	10
	Mean (SD)	-7.608 (3.1806)	-3.476 (1.0086)	-3.374 (2.9000)	-3.180 (3.5530)	-3.573 (1.2560)	-6.589 (0.8828)	-6.426 (2.0355)	-6.599 (3.3077)	-4.544 (3.2207)
	Median (Min, Max)	-8.237 (-11.55, -2.16)	-3.889 (-4.14, -1.98)	-2.873 (-8.75, 0)	-2.491 (-8.92, 0)	-3.573 (-4.46, -2.68)	-6.454 (-7.74, -5.71)	-5.857 (-9.91, -4.50)	-7.188 (-11.55, -2.16)	-5.442 (-8.92, 0)
Day 29	N	6	4	6	6	2	4	6	8	10
	Mean (SD)	-7.608 (3.1806)	-3.626 (0.7129)	-3.374 (2.9000)	-3.180 (3.5530)	-3.573 (1.2560)	-7.224 (0.9501)	-5.493 (1.8601)	-6.599 (3.3077)	-4.798 (3.4171)
	Median (Min, Max)	-8.237 (-11.55, -2.16)	-3.889 (-4.14, -2.58)	-2.873 (-8.75, 0)	-2.491 (-8.92, 0)	-3.573 (-4.46, -2.68)	-7.257 (-8.25, -6.13)	-5.816 (-7.43, -2.49)	-7.188 (-11.55, -2.16)	-5.654 (-8.92, 0)

Source: Table 2.3. Negative viral load results have been imputed as zero to align with the approach of the sponsor.

7.3.2. Time to Negative Viral Titers

The time to negative SARS-CoV-2 titers was assessed in participants in Phase 1 and Phase 2a of AGILE. In Phase 1, all participants receiving 50, 150 and 500 mg VIR-7832 (N=6 per dose group) achieved negative viral titers by Day 15, Day 8 and Day 8, respectively (Table 11). All participants receiving placebo in Phase 1 achieved negative viral titers by Day 22.

In Phase 2a, all participants receiving 500 mg VIR-7832 (N=4) achieved negative viral titer at Day 15 (Table 11). The participants receiving 500 mg VIR-7831 (N=6) and placebo (N=2) achieved negative viral titers at Day 11 and Day 8, respectively (Table 11).

Table 11 Summary of Time to Negative Nasal SARS-CoV-2 RNA

Visit	Viral Load Result	Phase 1				Phase 2a			Phase 1 + Phase 2a	
		Placebo, (N=6) n (%)	VIR-7832 50 mg (N=6) n (%)	VIR-7832 150 mg (N=6) n (%)	VIR-7832 500 mg (N=6) n (%)	Placebo, (N=2) n (%)	VIR-7832 500 mg (N=4) n (%)	VIR-7831 500 mg (N=6) n (%)	Placebo, (N=8) n (%)	VIR-7832, 500 mg (N=10) n (%)
Baseline	Positive	6 (100%)	5 (83%)	5 (83%)	4 (67%)	2 (100%)	4 (100%)	6 (100%)	8 (100%)	8 (80%)
	Negative	0	0	1 (17%)	2 (33%)	0	0	0	0	2 (20%)
	Missing	0	1 (17%)	0	0	0	0	0	0	0
Day 3	Positive	6 (100%)	5 (83%)	3 (50%)	3 (50%)	2 (100%)	4 (100%)	5 (83%)	8 (100%)	7 (70%)
	Negative	0	1 (17%)	3 (50%)	3 (50%)	0	0	0	0	3 (30%)
	Missing	0	0	0	0	0	0	1 (17%)	0	0
Day 5	Positive	6 (100%)	3 (50%)	1 (17%)	2 (33%)	2 (100%)	4 (100%)	4 (67%)	8 (100%)	6 (60%)
	Negative	0	3 (50%)	5 (83%)	4 (67%)	0	0	2 (33%)	0	4 (40%)
	Missing	0	0	0	0	0	0	0	0	0
Day 8	Positive	3 (50%)	0	0	0	0	2 (50%)	3 (50%)	3 (38%)	2 (20%)
	Negative	3 (50%)	4 (67%)	6 (100%)	6 (100%)	2 (100%)	2 (50%)	3 (50%)	5 (63%)	8 (80%)
	Missing	0	2 (33%)	0	0	0	0	0	0	0
Day 11	Positive	2 (33%)	1 (17%)	0	0	0	2 (50%)	0	2 (25%)	2 (20%)
	Negative	4 (67%)	5 (83%)	6 (100%)	6 (100%)	2 (100%)	2 (50%)	6 (100%)	6 (75%)	8 (80%)
	Missing	0	0	0	0	0	0	0	0	0
Day 15	Positive	1 (17%)	0	0	0	0	0	0	1 (13%)	0
	Negative	5 (83%)	6 (100%)	6 (100%)	6 (100%)	2 (100%)	4 (100%)	6 (100%)	7 (88%)	10 (100%)
	Missing	0	0	0	0	0	0	0	0	0
Day 22	Positive	0	0	0	0	0	0	0	0	0
	Negative	6 (100%)	6 (100%)	6 (100%)	6 (100%)	2 (100%)	4 (100%)	6 (100%)	8 (100%)	10 (100%)
	Missing	0	0	0	0	0	0	0	0	0
Day 29	Positive	0	0	0	0	0	0	0	0	0
	Negative	6 (100%)	6 (100%)	6 (100%)	6 (100%)	2 (100%)	4 (100%)	6 (100%)	8 (100%)	10 (100%)
	Missing	0	0	0	0	0	0	0	0	0

Source: Table 2.2. Percentages are based on number of participants in treatment arm. A component (Gene-N, Gene-S, ORF1) is considered as having negative viral load if a subject has two consecutive results where the cycle threshold value ≥32. A subject is assigned as having overall negative SARS-CoV-2 PCR if at least two of these three components are negative.

7.3.3. Area Under of the Curve for SARS-CoV-2 Viral RNA Levels

The AUCs of SARS-CoV-2 viral load (log_{10} copies/mL) both from Day 1 to Day 8 (Table 12) and Day 1 to Day 29 (Table 13) were determined for participants in Phase 1 and Phase 2a of the clinical study.

The geometric mean $AUC_{(D1-8)}$ was similar for participants receiving 50, 150 and 500 mg VIR-7832 in Phase 1, ranging from 4.61-7.18, as compared to that of the participants receiving placebo which was 19.91 (Table 12). The geometric mean $AUC_{(D1-29)}$ was also similar for participants receiving 50, 150 and 500 mg VIR-7832 in Phase 1, ranging from 4.61-10.64, as compared to that of the participants receiving placebo which was 24.18 (Table 13).

The geometric mean $AUC_{(D1-8)}$ for participants receiving 500 mg VIR-7832 in Phase 2a was 26.32 as compared that of participants receiving placebo (15.35) or VIR-7831 (16.69) (Table 12). The geometric mean $AUC_{(D1-29)}$ for participants receiving 500 mg VIR-7832 in Phase 2a was 36.23 as compared that of participants receiving placebo (15.35) or VIR-7831 (8.57) (Table 13).

Table 12 Summary of $AUC_{(D1-8)}$ of SARS-CoV-2 Viral Load (log_{10} copies/mL) as Measured by qRT PCR from Nasal Swabs

Parameter	Viral Load Result	Phase 1				Phase 2a			Phase 1 + Phase 2a	
		Placebo (N=6)	VIR-7832 50 mg (N=6)	VIR-7832 150 mg (N=6)	VIR-7832 500 mg (N=6)	Placebo (N=2)	VIR-7832 500 mg (N=4)	VIR-7831 500 mg (N=6)	Placebo (N=8)	VIR-7832 500 mg (N=10)
AUC (D1-8)	N	6	4	5	4	2	4	5	8	8
	Geometric Mean	19.91	6.69	4.61	7.18	15.35	26.32	16.69	18.65	13.75
	95% CI	(7.71, 51.41)	(3.53, 12.67)	(2.12, 10.03)	(2.31, 22.30)	(0.59, 396.45)	(13.59, 51.00)	(8.95, 31.12)	(9.67, 35.97)	(6.59, 28.68)
	SD (log)	0.904	0.402	0.626	0.712	0.362	0.416	0.502	0.785	0.88
	% CVb	112.427	41.855	69.218	81.266	37.408	43.418	53.519	92.365	108.051

Source: Table 2.4. AUC values of zero have been excluded from this summary.

Table 13 Summary of $AUC_{(D1-29)}$ of SARS-CoV-2 Viral Load (log_{10} copies/mL) as Measured by qRT PCR from Nasal Swabs

Parameter	Viral Load Result	Phase 1				Phase 2a			Combined Phase 1 + Phase 2a	
		Placebo, (N=6)	VIR-7832 50 mg (N=6)	VIR-7832 150 mg (N=6)	VIR-7832 500 mg (N=6)	Placebo, (N=2)	VIR-7832 500 mg (N=4)	VIR-7831 500 mg (N=6)	Placebo, (N=8)	VIR-7832, 500 mg (N=10)
AUC (D1-29)	N	6	4	5	4	2	4	6	8	8
	Geometric Mean	24.18	10.64	4.61	7.18	15.35	36.23	8.57	21.58	16.13
	95% CI	(10.27, 56.94)	(2.60, 43.52)	(2.12, 10.03)	(2.31, 22.30)	(0.59, 396.45)	(16.49, 79.64)	(0.83, 88.57)	(11.68, 39.86)	(6.79, 38.31)
	SD (log)	0.816	0.885	0.626	0.712	0.362	0.495	2.226	0.734	1.035
	% CVb	97.315	109.018	69.218	81.266	37.408	52.682	1187.127	84.504	138.493

Source: Table 2.4. AUC values of zero have been excluded from this summary.

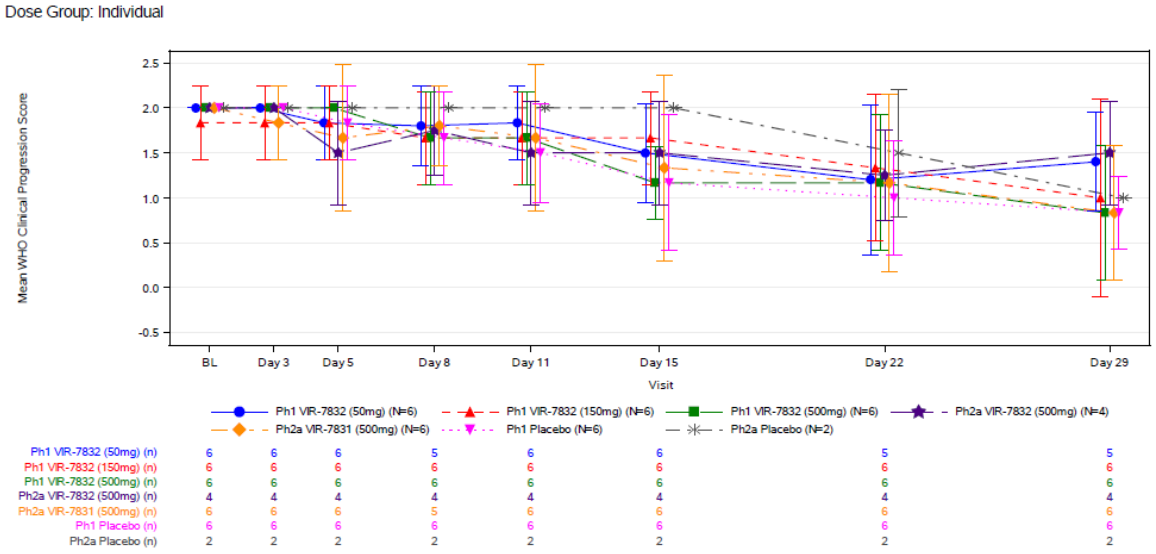
7.4. Clinical

7.4.1. WHO Clinical Progression Score

There was a mean trend decrease (with observed variability) over time in WHO Clinical Progression Score, indicating an improvement in illness severity over time for each treatment cohort (Figure 6).

All participants had WHO Clinical Progression Scores <3 (indicating mild COVID-19 disease) at all time points measured. Although 2 participants were hospitalized within 29 after treatment administration, their progression scores did not reflect COVID-19 worsening. In addition, no participants in any arm required supplemental oxygen administration, and all oxygen saturations remained at ≥94% throughout Day 29 assessments (Source Table 2.5).

Figure 6 Plot of Mean (+/-SD) WHO Clinical Progression Score by Visit (ITT Population)



Source: Figure 2.1
Abbreviations: Ph=Phase

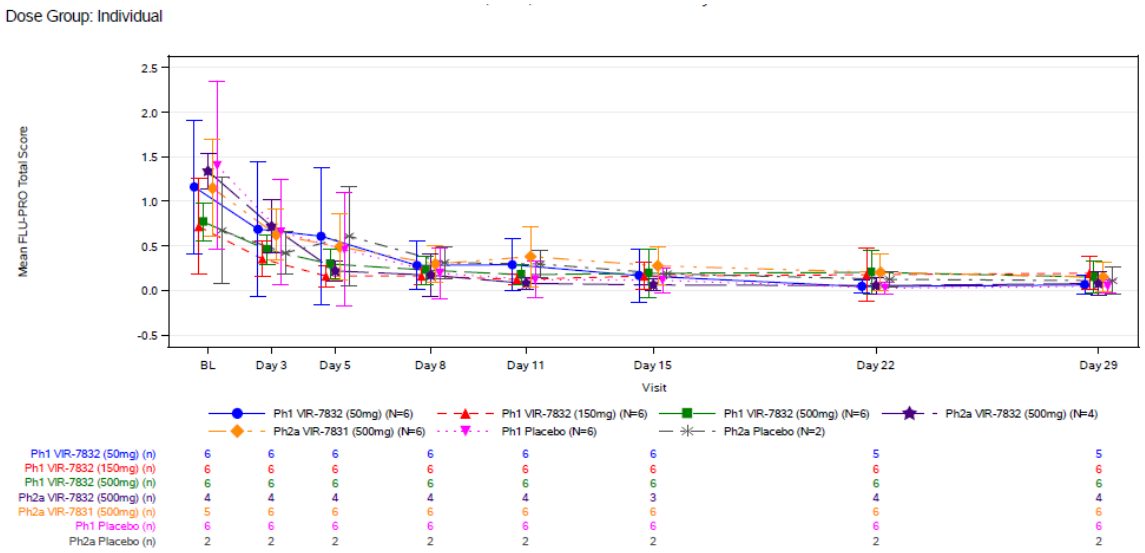
7.4.2. NEWS2 Score

There was variability around mean NEWS2 score estimates. Generally, no trend was observed over time in all treatment groups (Source: Table 2.5).

7.4.3. FLU- Pro Total Score

There was a decreasing trend (with observed variability) over time in all treatment groups for FLU-PRO Total Score, indicating improvement in severity of symptoms for each treatment cohort (Figure 7). These decreases similar between treatment and placebo (Source: Table 2.6).

Figure 7 Plot of Mean (+/-SD) FLU-PRO Total Score by Visit (ITT Population)



Source: Figure 2.3
Abbreviations: Ph=Phase

8. CONCLUSIONS

Safety

- The safety data from this study suggest a favorable tolerability profile of VIR-7832 (GSK4182137) and VIR-7831 (sotrovimab; GSK4182136) in adult participants for treatment of COVID-19.

PK

- The geometric mean of the estimated steady state volume of distribution ranging 6-7 L for VIR-7832 indicates limited distribution outside the vascular space, which is consistent with other IgGs. The long half-life (40-50 days) observed for VIR-7832 is consistent with the addition of the half-life extending LS mutation.
- Exposures following 500 mg and 150 mg IV VIR-7832 were approximately 10x and 3x the exposure observed following 50 mg IV dose of VIR-7832, respectively, which indicates dose proportionality over the dose range of 50-500 mg. However, formal dose proportionality analysis was not performed.

Immunogenicity

- There was no apparent impact of ADA on VIR-7831or VIR7832 exposure or safety.

Virology

- The levels of SARS-CoV-2 RNA decreased over time for participants receiving VIR-7832 in Phase 1 and Phase 2a.
- All participants receiving VIR-7832 in Phase 1 or Phase 2a achieved negative viral titer by Day 15.
- The geometric mean $AUC_{(D1-8)}$ and $AUC_{(D1-29)}$ of SARS-CoV-2 viral load was similar for participants receiving 50, 150 and 500 mg VIR-7832 in Phase 1.
- Comparisons for absolute viral load, change from baseline in viral load, time to negative viral titer and AUC for viral load between VIR-7832 dose groups and participants receiving placebo or comparator (VIR-7831) were not done due to small numbers of participants and differences in baseline viral load in each group.

Clinical

- The FLU-PRO and WHO Clinical Progression Scores showed improvement over time in all the treatment groups, with no apparent differences between active and placebo treatments. These results and the small sample size preclude drawing definitive conclusions about the role of VIR-7832 or VIR-7831 in reducing the risk of COVID-19 progression.

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10. CASE NARRATIVES

There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data comes from 2 different databases (i.e., locked clinical trials database and dynamic SAE database) and has been collected at different points in time. However, all key data points are reconciled. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

2022-VIR00002-GB VIR-7832-5101 (Phase 2) "VR21001001" NSTEMI secondary to coronary artery disease, Coronary artery bypass graft, Bilateral pleural effusion, Acute kidney injury, Sternal wound infection

Initial information received on 04-May-2022:

Participant VR21001001 (confirmed), a 52-year-old female participant of unknown race was enrolled in the University of Liverpool sponsored study VIR-7832-5101 (AGILE CST-5), titled "A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2a Platform Study to Determine the Phase 2a Dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19".

The participant's relevant medical history included tachycardia, diabetes ongoing since 01-Jan-1997 (type 2 diabetes mellitus, poorly controlled diabetes mellitus), hypertensive risk factors for non-ST elevation myocardial infarction (NSTEMI) and COVID infection.

Concomitant medications taken at the time of the event included candesartan (16mg, orally, frequency unknown, ongoing since 1997) for unreported indication, amlodipine (5mg, orally, frequency unknown, ongoing since 14-Apr-2022) for unreported indication, atorvastatin (40mg, orally, frequency unknown, ongoing since 2009) for unreported indication, clopidogrel (75mg, orally, frequency unknown, ongoing since 2016) for unreported indication, dapagliflozin (10mg, orally, frequency unknown, ongoing since 2018) for unreported indication, humalog insulin (60 units, subcutaneously, frequency unknown, ongoing since 2007) for unreported indication, indomethacin (25mg, orally, frequency unknown, ongoing since 1999) for unreported indication, lansoprazole (15mg, orally, frequency unknown, ongoing since 2017) for unreported indication, Lantus insulin (insulin glargine) (50 units, subcutaneously, frequency unknown, ongoing since 2021) for unreported indication, levothyroxine (125µg, orally, frequency unknown, ongoing since 2007) for unreported indication, mebeverine (135mg, orally, frequency unknown, taking from Jan-2021 to 03-May-2022) for unreported indication, and Cerelle (desogestrel) (75mg, orally, frequency unknown, ongoing since 2007) for unreported indication; candesartan 8 mg,qd oral since 08-Aug-2022 for unknown indications, amlodipine 10mg oral since 23-Jun-2022 for unknown indications, atorvastatin 80 mg oral since 02-May-2022 for unknown indications, lansoprazole 30 mg oral since 23-Jun-2022 for unknown indication, Lantus (insulin glargine) 40 mg subcutaneous since 23-Jun-2022 for unknown indications, bisoprolol 6.25 mg qd since 09-Jun-2022 for unknown indications, aspirin E.C 75 mg qd since 03-May-2022 for unknown indications, aflibercept 2 mg on 05-Nov-

2022, route of administration other for unknown indications, influenza vaccine on 22-Oct-2022, route of administration other for unknown indications. The investigator reported that concomitant medications candesartan, amlodipine, atorvastatin, clopidogrel, dapagliflozin, humalog insulin, indomethacin, lansoprazole, Lantus insulin, levothyroxine, mebeverne, and Cerelle were reported as treatment for coronary artery bypass graft (CABG).

On 25-Apr-2022, the participant received her initial dose of blinded study drug intravenously at 500 MG and unknown frequency. This initial dose was also her most recent dose prior to SAE onset.

On 26-Apr-2022, the participant had memo device fitted to monitor her heart rate and rhythm.

On 02-May-2022, 7 days following her initial dose of the blinded study drug, the participant experienced NSTEMI secondary to coronary artery disease (PT: Acute myocardial infarction). The site reported that the participant had been under investigation for palpitations for the last six weeks. On 02-May-2022, the participant started to experience more frequent palpitations than usual and some left-sided intermittent chest pain. The participant called 111 who advised attendance at accident and emergency (A&E).

The laboratory results revealed slight changes on her electrocardiography (ECG) ST elevation on lead 3 and depression on lead 1; troponin tests performed on 02-May-2022 showed 66 ng/L (at 18:03) and 94 ng/L (at 21:16) (reference range: 0 – 18 ng/L).

On 02-May-2022, the participant was admitted to the coronary care unit where the working diagnosis was perimyocarditis +/- NSTEMI. On 02-May-2022, echocardiogram was performed which excluded perimyocarditis.

On 18-May-2022, the coronary angiogram diagnostic test was performed, which confirmed vessel disease causing NSTEMI with severe left circumflex artery and left anterior descending (CIR + LAD).

On 31-May-2022, 36 days following her initial dose of the blinded study drug, the participant underwent a coronary artery bypass graft (CABG) (PT: Coronary artery bypass) to treat NSTEMI; surgery prolonged hospitalization. The investigator confirmed onset of CABG was on 31-May-2022.

On 31-May-2022, CABG was considered resolved.

On 01-Jun-2022, 37 days following her initial dose of the blinded study drug, the participant returned to cardiac intensive care unit following CABG and was found to have bilateral pleural effusion (PT: Pleural effusion) and acute kidney injury (PT: Acute kidney injury) secondary to post op complications of coronary artery bypass graft for acute myocardial infarction, which resulted in prolongation of the hospitalization. On 01-

Jun-2022, chest x-ray revealed “not formally reported but evidence of bilateral pleural effusion” and renal function test showed “creatinine 310 UMOL/L (references range: 53-97 UMOL/L). On 01-Jun-2022, the participant was started with intravenous (IV) furosemide due to pleural effusion. The acute kidney injury was managed with intravenous fluids.

On 01-Jun-2022, the participant had discharge/infection from sternotomy wound.

On 10-Jun-2022, chest x-ray revealed “worsening bilateral pleural effusion”. As a result of poor pleural resolution, right sided chest drain was inserted to aid the resolution.

On 18-Jun-2022, chest x-ray revealed improving bilateral pleural effusion with marked improvement on right side.

On 19-Jun-2022, acute kidney injury was considered recovered/resolved.

On 20-Jun-2022, bilateral pleural effusion was considered improved and not completely resolved. The chest drain was removed, and furosemide was changed from IV to oral.

On 23-Jun-2022, bilateral pleural effusion and coronary artery bypass graft were considered recovered/resolved, NSTEMI secondary to coronary artery disease was considered recovered/resolved with sequelae of shortness of breath and chest pain, and the participant was discharged from hospital with medication to optimize her cardiovascular function post CABG.

On 15-SEP-2022, the participant was reviewed in clinic and reported that she was increasing her activity levels without any shortness of breath or chest pain hence her sequelae had resolved, and she was discharged from cardiothoracics.

The participant was treated home with oral antibiotics, several courses, since 22-Aug-2022, however the participant had ongoing symptoms from discharge/infection from sternotomy wound, therefore the participant was admitted to the hospital on 03-Dec-2022 for IV antibiotics and possible wound debridement.

The investigator confirmed that all of the SAE of NSTEMI secondary to coronary artery disease, bilateral pleural effusion and acute kidney injury as CTCAE grade 3 (severe) occurred during the same hospital stay from 02-May-2022 to 23-Jun-2022.

On 03-Dec-2022, 222 days following her initial dose of the blinded study drug, the participant developed sternal wound infection (PT: Wound infection).

On 03-Dec-2022, the participant’s CT scan revealed "soft tissue thickening and no convincing collection", CRP was 44 milligram per litre (reference range: 0-7.5 milligram per litre), white blood cell count 11.8 billion per litre (reference range: 4.0 - 11.0 billion per litre) and neutrophil count 8.0 billion per litre (reference range: 2.0-7.5 billion per litre). The investigator reported wound healing may have been impacted by poorly controlled diabetes.

On 09-Dec-2022, the participant was admitted to the hospital for sternal wound debridement. The investigator reported that VAC dressing was applied and changed, and skin swab was taken.

On 14-Dec-2022, the participant's CT chest confirmed no collection and the participant was discharged with a plan to return for wound review. The investigator reported that VAC dressing was removed, no growth was found on skin swab, and the wound was closed.

On 14-Dec-2022, the sternal wound infection was considered resolved.

There was no change to the dosing schedule due to the events of NSTEMI secondary to coronary artery disease, coronary artery bypass graft, bilateral pleural effusion and acute kidney injury and sternal wound infection.

No action was taken regarding the study drug.

The investigator assessed the events of NSTEMI secondary to coronary artery disease, coronary artery bypass graft, bilateral pleural effusion, acute kidney injury, and sternal wound infection as CTCAE grade 3 (severe) and not related to the blinded study drug. The events were serious based on hospitalization. The investigator assessed the event of NSTEMI secondary to coronary artery disease as related to medical history since the participant was under investigation for tachycardia prior to the study. The participant was also diabetic and hypertensive, risk factors for NSTEMI and recent COVID infection is a risk factor for peri-myocarditis. The investigator assessed the event of coronary artery bypass graft as not related the blinded study drug, because the event CABG was part of treatment following NSTEMI due to severe coronary artery disease. The investigator assessed the event of bilateral pleural effusion as related to NSTEMI and acute kidney injury was secondary to post op complications of coronary artery bypass graft for acute myocardial infarction. The investigator assessed the event sternal wound infection as related to type 2 diabetes mellitus and coronary artery bypass graft.

Sponsor Clinical Reviewers assessment: Sponsor Clinical reviewers assessed the event NSTEMI secondary to coronary artery disease as not related to the blinded study drug. The clinical reviewer further commented that participant was at high risk for cardiac disease on basis of medical history with pre-existing investigation. The coronary artery bypass graft was assessed as not related to the blinded study drug. The assessment for event bilateral pleural effusion is likely related to heart failure and post-surgical complication. The bilateral pleural effusion was assessed as not related to the blinded study drug. The acute kidney injury was assessed as not related to the blinded study drug. The sternal wound infection was assessed as not related to the blinded study drug.

The reviews of the events NSTEMI secondary to coronary artery disease, bilateral pleural effusion, and sternal wound infection were carried out blinded by the clinical reviewer. It was confirmed that the assessment was made while the participant and study team remain

blinded. The review for the event of acute kidney injury was carried out unblinded by the clinical reviewer.

Company assessment: Vir Biotechnology agrees with the investigator's assessment of severity and causality as not related to blinded study drug. The event of acute myocardial infarction is considered unexpected per the current Investigator's Brochure. The event of coronary artery bypass is considered unexpected per the current Investigator's Brochure. The event of bilateral pleural effusion is considered unexpected per the current Investigator's Brochure. The event of acute kidney injury is considered unexpected per the current Investigator's Brochure. The event of sternal wound infection is considered unexpected per the current Investigator's Brochure.

Follow-up information received on 16-May-2022, 17-May-2022 and 18-May-2022:

Follow-up information included update of event term from PERIMYOCARDITIS + POSSIBLE NON ST ELEVATION MYOCARDIAL INFARCTION to PERIMYOCARDITIS + POSSIBLE NON ST ELEVATION MYOCARDIAL INFRACTION 13/05/2022 CORONARY ARTERY DISEASE. The site provided confirmation that participant remains hospitalized and event outcome as ongoing, and details regarding site number, participant's year of birth, concomitant medications causal relationship and study drug administration details. The clinical reviewers' assessment of the event was also provided.

Follow-up information received on 27-May-2022 and 30-May-2022:

Follow-up information included update of event term from PERIMYOCARDITIS + POSSIBLE NON ST ELEVATION MYOCARDIAL INFRACTION 13/05/2022 CORONARY ARTERY DISEASE to NSTEMI secondary to coronary artery disease.

The site provided confirmation that the clinical reviewer's assessment for the event remains the same. The site also confirmed that there is no information regarding participant's ethnicity.

Follow-up information received on 08-Jun-2022:

Follow-up information included the date and outcome of the coronary angiogram diagnostic test performed.

Follow-up information received on 21-Jun-2022 and 22-Jun-2022:

Follow-up information included the date and type of surgery performed for NSTEMI and provided the diagnostic test results (chest x-ray) and details of a new serious adverse event of right pleural effusion.

Follow-up information received on 29-Jun-2022, 30-Jun-2022, 01-Jul-2022 and 04-Jul-2022.

Follow-up information included the end date for the event of NSTEMI secondary to coronary artery disease and right pleural effusion. The event of perimyocarditis was confirmed to be ruled out and not a SAE and a serious adverse event of acute kidney injury was reported.

Follow-up information received on 06-Jul-2022 and 12-Jul-2022:

Follow-up information included an update of the event term from “right pleural effusion” to “bilateral pleural effusion,” confirmation that NSTEMI was due to “coronary artery disease,” and the participant has no previous history of coronary artery disease. Clinical reviewers’ assessment of the event “acute kidney injury” was also provided.

Follow-up information received on 14-Jul-2022:

Upon review, no significant new information was provided. Non-significant new information included: clinical reviewer confirmed that the clinical review provided on 12-Jul-2022 was performed while blinded.

Follow-up information received on 01-Aug-2022:

Follow-up information included an update to the renal function test from 01-Jun-2022 with unit provided for the “creatine” result.

Follow-up information received on 05-Aug-2022 and 08-Aug-2022:

Upon review, no significant new information was provided. Non-significant new information included: Update of event outcome of Bilateral Pleural Effusion to resolved in order to align with the date of resolution provided previously. Correction was also performed for dosage of study drug administered.

Follow-up information received on 12-Aug-2022:

Follow-up information included an update of the renal function test result from “creatine” to “creatinine” and the reference range was 55-97.

Follow-up information received on 19-Aug-2022:

Follow-up information included hospital discharge dates for the SAEs, diagnostic test results relevant to the events NSTEMI secondary to coronary artery disease and acute kidney injury, and confirmation that “CIRC” in the coronary angiogram results on 18-May-2022 stands for “circumflex artery”. The site also confirmed that for the reported event of NSTEMI secondary to coronary artery disease, NSTEMI is the main event and coronary artery disease is AE and not a separate SAE.

Follow-up information received on 21-Sep-2022 and 26-Sep-2022:

Upon review, no significant new information was provided on 21-Sep-2022. Follow-up information provided on 26-Sep-2022 included confirmation of event onset date as the date the events met seriousness criteria (hospitalization) on 01-Jun-2022.

Follow-up information received on 04-Oct-2022:

Follow-up information stated that all of the SAEs occurred during the same hospital stay; date of hospitalization and date discharged from hospital for all SAEs were updated.

Follow-up information received on 06-Dec-2022(Day 0) and additional information received on 06-Dec-2022, 07-Dec-2022 and 09-Dec-2022:

SAE sternal wound infection was added; concomitant medications were updated; details for the previously reported SAE acute kidney injury were reported with no new information; study drug was updated from unknown to "IMP/PLACEBO" for the SAE of sternal wound infection.

Follow-up information received on 14-Dec-2022 (Day 0) and additional information received on 15-Dec-2022:

Follow-up information included updated outcome, event end date, hospitalization dates, treatment details, CT result, clinical course, and the clinical reviewer’s opinion for the event of sternal wound infection.

Follow-up information received on 30-Dec-2022 (Day 0) and additional information received on 04-Jan-2023:

Follow-up information included onset date of diabetes, etiology of acute kidney injury as secondary to post op complications of coronary artery bypass graft for acute myocardial infarction, and updated event term from burst cyst on scar line (sternotomy) to sternal wound infection.

Follow-up information received on 06-Jan-2023 and additional information received on 09-Jan-2023 and 10-Jan-2023:

The clinical reviewer and primary investigator confirmed that the causality assessment was not related for the event sternal wound infection (previously reported), the sequelae of NSTEMI and final outcome of NSTEMI were reported, echocardiogram was performed on 02-May2022, which excluded perimyocarditis.

Follow-up information received on 26-Jan-2023 (Day 0) and additional information received on 27-Jan-2023:

Follow-up information received as causality description was updated from non factors for NSTEMI to risk factors for NSTEMI, investigator confirmed that study drug was administered for one day as confirmed in EDC source document for NSTEMI number of days on treatment was updated from 8 to 1, EDC source document for acute kidney injury

number of days on treatment was updated from 56 to 1, and EDC source document for bilateral pleural effusion number of days on treatment was updated from 56 to 1.

Non-significant Follow-up information received on 22-Feb-2023:

No new safety information received.

Investigator confirmed bilateral pleural effusion was resolved (previously reported).

Follow-up information received on 27-Feb-2023 (Day 0) and additional information received on 28-Feb-2023 and 01-Mar-2023:

Follow-up information included details of additional SAE of coronary artery bypass graft and confirmation of the participant number, duplicate information of non-significant follow-up on 22-Feb-2023 received on 01-Mar-2023.

Follow-up information received on 08-Mar-2023:

Follow-up information included details of SAE of coronary artery bypass graft (previously reported), date CABG was resolved with sequelae, and the causality of event CABG was related to concomitant medications.

Non-Significant Follow-up received on 23-MAR-2023 and Additional information on 24-MAR-2023:

Follow-up information includes the investigator reconfirming the event CABG caused prolongation hospitalization and the event of CABG on ended on 31-May-2022.

Follow-up information received on 29-Mar-2023 (Day 0):

Follow-up information included outcome the event coronary artery bypass graft was updated from resolved with sequelae to resolved, confirmed CABG onset date (31-May-2022), and updated alternate causality for CABG

Follow-up information received on 21-Jun-2023 (Day 0):

Follow-up information included updated date of outcome of resolved with sequelae for event of NSTEMI to 23-Jun-2022 (previously reported as 31-May-2022).

COMPANY COMMENT:

The investigator assessed the Acute myocardial infarction as Not Related to study drug VIR-7831 vs VIR-7832 vs Placebo. Based on information currently available for this case, notably the participant was at high risk for cardiac disease on the basis of medical history (hypertension and diabetes), with pre-existing tachycardia which was under investigation, Vir Biotechnology assessed that there is not a reasonable possibility of a

causal association and therefore the SAE of Acute myocardial infarction is considered Not Related to VIR-7831 vs VIR-7832 vs Placebo.

The investigator assessed the Coronary artery bypass as Not Related to study drug VIR-7831 vs VIR-7832 vs Placebo. Based on information currently available for this case, notably the participant was at high risk for cardiac disease on the basis of medical history (hypertension and diabetes), the participant experienced NSTEMI (acute myocardial infarction) secondary to coronary artery disease, and underwent coronary artery bypass graft (for acute myocardial infarction/NSTEMI secondary to coronary artery disease), Vir Biotechnology assessed that there is not a reasonable possibility of a causal association and therefore the SAE of Coronary artery bypass is considered Not Related to VIR-7831 vs VIR-7832 vs Placebo.

The investigator assessed the Pleural effusion as Not Related to study drug VIR-7831 vs VIR-7832 vs Placebo. Based on information currently available for this case, notably heart failure and post-surgical complication from coronary artery bypass graft (for acute myocardial infarction), Vir Biotechnology assessed that there is not a reasonable possibility of a causal association and therefore the SAE of Pleural effusion is considered Not Related to VIR-7831 vs VIR-7832 vs Placebo.

The investigator assessed the Acute kidney injury as Not Related to study drug VIR-7831 vs VIR-7832 vs Placebo. Based on information currently available for this case, notably prior coronary artery bypass graft procedure (for acute myocardial infarction) (acute kidney injury is a common complication after coronary artery bypass grafting) and underlying diabetes mellitus, Vir Biotechnology assessed that there is not a reasonable possibility of a causal association and therefore the SAE of Acute kidney injury is considered Not Related to VIR-7831 vs VIR-7832 vs Placebo.

The investigator assessed the Wound infection as Not Related to study drug VIR-7831 vs VIR-7832 vs Placebo. Based on information currently available for this case, notably poorly controlled diabetes mellitus and prior coronary artery bypass graft procedure (for acute myocardial infarction) associated with discharge/infection from sternotomy wound, Vir Biotechnology assessed that there is not a reasonable possibility of a causal association and therefore the SAE of Wound infection is considered not related to VIR-7831 vs VIR-7832 vs Placebo.

The Acute myocardial infarction, Coronary artery bypass, Pleural effusion, Acute kidney injury, and Wound infection were assessed as Unexpected per the current Investigator's Brochure.

The information provided in this individual case does not warrant a change to the Investigator's Brochure and does not constitute an unanticipated problem or urgent safety measure at this time. This topic will continue to be monitored closely.

2021-VIR00001-GB VIR-7832-5101 "1049-002" Dyspnoea

Case Description: Initial information received on 14-Jun-2021 and 17-Jun-2021:

Participant 1049-002, a 28-year-old male was enrolled in the VIR-7832-5101 (AGILE CST-5) study, titled “A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2a Platform Study to Determine the Phase 2a Dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19".

The participant’s relevant medical history included COVID-19. No concomitant medications were taken.

On 03-Jun-2021, the participant received the first and only dose of blinded study drug at 50 mg for one day. This initial dose was also his most recent dose prior to SAE onset.

On 11-Jun-2021, Day 9 after receiving the blinded study drug, the participant developed dyspnoea (PT: Dyspnoea) (Severity: CTCAE Grade 2). The event was progressive worsening; chest tightness (Grade 2) and productive cough (Grade 1) were reported as associated symptoms. Examination of the chest was normal. There were no abnormalities on CUS, abdominal examination.

On 11-Jun-2021, the participant was hospitalized and admitted to infectious diseases (ID) unit due to concerns of worsening COVID-19, pneumonitis, or pulmonary embolism. Initial investigations included full blood count, biochemistry panel, c-reactive protein (CRP), D-dimer, and chest x-ray. Vital signs were normal and oxygen saturation on air was of 99%. The participant was observed overnight. Oxygen saturations remained between 95-99% overnight on room air. The participant had no fever.

On 11-Jun-2021, laboratory tests included: CRP 5 mg/L (reference range: 0 – 4), very mild elevation (not clinically significant) and D-dimer 441 ng/mL (reference range: 0 – 500), normal, therefore pulmonary embolism was considered unlikely, and chest x-ray on admission was normal, did not reveal any evidence of COVID-pneumonitis.

On 12-Jun-2021, chest x-ray was normal.

On 12-Jun-2021, the participant was reviewed by ID consultant. The participant was felt to have ongoing COVID-19 symptoms and was discharged home with normal oxygen saturations (remained 98-99% on room air), chest x-ray, CRP, and D-dimer. The participant was noted to have some intrusive thoughts of self-harm and was reviewed by the mental health team prior to his discharge; this has been reported as a separate adverse event. The investigator reported this was not considered an SAE and therefore not reported as one (it did not lead to the participant's admission or meet any other SAE criteria).

On 12-Jun-2021, the event of dyspnoea was resolved. No action for the blinded study drug was taken due to the event. Both associated symptoms, chest tightness and productive cough were also resolved on 12-Jun-2021.

The investigator assessed the event of dyspnoea as not related to the blinded study drug. The investigator considered the event of dyspnoea to be caused by COVID-19. The investigator reported the impression of both the research team and ID team treating the participant at the time of the SAE and the participant reported shortness of breath at his screening assessment, consequently COVID-19 was a reasonable explanation for his presentation and other, alternative pathologies were ruled out based on normal chest x-ray, D-Dimer and oxygen saturations.

The clinical reviewer for the study assessed the event of dyspnoea as not related to the blinded study drug and considered the event of dyspnoea highly likely related to COVID infection.

Company assessment: The Sponsor agrees with the investigator's assessment of causality. The event of dyspnoea is considered unexpected per the current Investigator's Brochure, Edition 1, 03-Dec-2020.

Follow-up information received on 24-Jun-2021 and 25-Jun-2021:

Follow-up information includes eCRF with assessment provided by the clinical reviewer for the study at SCTU and paper SAE report form updating the event onset date.

Follow-up information received on 30-Jun-2021:

Follow-up information includes updated eCRF with diagnostic tests result. The updated electronic forms provide no new information.

Follow-up information received on 27-Jan-2023:

Follow-up information included the investigator confirmation that study drug was administered for one day as confirmed in EDC source document for dyspnoea the number of days on treatment was updated from 9 to 1.

Non-significant Follow-up information received on 22-Feb-2023:

No new safety information provided. Investigator confirmed participant did not receive any concomitant medications, had relevant medical history of COVID-19 and details of treatment administered for the SAE (previously reported), test results were already provided, and investigator will request information from site regarding the thoughts of self-harm being an additional SAE, rationale dyspnoea was caused by Covid-19, and will ask for confirmation if pneumonitis and pulmonary embolism were excluded.

Follow-up information received on 01-Mar-2023:

Follow-up information included the confirmation that the participant did not receive any concomitant medications (previously reported), relevant medical history of COVID-19 (previously reported), treatment details administered for the SAE (previously reported), diagnostic test results (previously reported), did not reveal any evidence of Covid-pneumonitis, pulmonary embolism was considered unlikely, rationale dyspnea was caused by COVID-19, and the investigator reported participant's thoughts of self-harm was not considered SAE.

Company Comment:

The investigator assessed the Dyspnoea as not related to the blinded study drug VIR-7832 vs Placebo.

The investigator reported alternate causality for the event was due to COVID-19. The investigator reported the impression of both the research team and ID team treating the participant at the time of the SAE and the participant reported shortness of breath at his screening assessment, consequently COVID-19 was a reasonable explanation for his presentation and other, alternative pathologies were ruled out based on normal chest x-ray, D-Dimer and oxygen saturations.

The event is confounded by the participant's underlying COVID-19. The participant additionally reported shortness of breath at his screening assessment. The SAE of Dyspnoea is considered Not Related to VIR-7832 or Placebo.

The Dyspnoea was assessed as unexpected for VIR-7832 vs Placebo as per the current Investigator's Brochure.

The information provided in this individual case does not warrant a change to the Investigator's Brochure and does not constitute an unanticipated problem or urgent safety measure at this time. This topic will continue to be monitored closely.

2022-VIR00001-GB VIR-7832-5101 (Phase 2) "VR2-1049007" Staphylococcus aureus bacteraemia

Initial information received on 30-Sep-2022:

Participant 1049-007, a 48-year-old male was enrolled in the University of Liverpool sponsored study VIR-7832-5101 (AGILE CST-5), titled "A Randomized, Multicentre, Seamless, Adaptive, Phase 1/2a Platform Study to Determine the Phase 2a Dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19".

The following medical history was reported: type 1 diabetes mellitus (dates not provided). The participant's most recent glycosylated haemoglobin (HbA1c) at the time

of the SAE (date not provided) was 84 IFCC mmol/mol (normal range: less than 42), which indicated relatively poor control of his diabetes in the 3 months prior to the event.

The participant did not take any concomitant medications including no treatment medications for type 1 diabetes mellitus.

On 14-Apr-2022, the participant received his initial and only dose of the blinded study drug at 500 mg for one day.

On 14-Apr-2022, the participant received his most recent dose of the blinded study drug at 500 mg.

On 07-Sep-2022, the participant developed fever and attended the emergency department (ED). Blood culture for Staphylococcus aureus was performed that day.

On 08-Sep-2022 (less than 24 hours in ED), the participant was reviewed and discharged without admission.

On 09-Sep-2022, 4 months and 27 days following his most recent dose of the study drug, the participant experienced Staphylococcus aureus bacteraemia (PT: Staphylococcal bacteraemia) (Severity: CTCAE grade 3). The event resulted in hospitalization. The participant was contacted for hospital admission on 09-SEP-2022 and was treated with intravenous (IV) flucloxacillin for Staphylococcus aureus bacteraemia. No source was identified after multiple investigations. The investigator also reported that event onset date was the date event met seriousness criteria.

On 12-Sep-2022, the final blood culture was reported as positive for Staphylococcus aureus.

On 13-Sep-2022, echocardiogram showed no evidence of infective endocarditis.

On 16-Sep-2022, computed tomography (CT) of thorax, abdomen and pelvis identified no source of infection while magnetic resonance imaging (MRI) of the right foot performed on 16-Sep-2022 showed no evidence of osteomyelitis.

On 20-Sep-2022, the Staphylococcus aureus bacteraemia was considered resolved and the participant was subsequently discharged to complete further outpatient antibiotics IV at home.

There was no change to the dosing schedule as a result of the event.

In Dec-2022, the participant’s most recent HbA1c was 89 (normal range: less than 42), which kept with the previous result of relatively poor control of diabetes.

The investigator assessed the event of Staphylococcus aureus bacteraemia as not related to the blinded study drug and reported that the likely cause of the event is the participant's medical history of type 1 diabetes.

The clinical reviewer also updated that the event of Staphylococcus aureus bacteraemia was unrelated to the blinded study drug.

Significant Follow up received on 11-Oct-2022 (Day 0):

New information received: Clinical Reviewer Opinion was updated.

Significant Follow up received on 14-Oct-2022(Day 0) and Additional information received on 17-Oct-2022:

New information received: Medical history, alternate causality, and the date of the final report for blood culture were provided.

Follow-up information received on 27-Jan-2023:

Follow up information included investigator confirmed that study drug was administered for one day as confirmed in EDC source document for Staphylococcus aureus bacteraemia the number of days on treatment was updated from 149 to 1.

Non-significant Follow-up information received on 22-Feb-2023:

No new safety information received. Investigator reported that site reported no treatment for type 1 diabetes mellitus (reported previously), event onset date was date event met seriousness criteria (reported previously), and that they would reach out to the site to confirm if diabetes was under control prior to onset of the event.

Follow-up information received on 01-Mar-2023:

Follow up information included no concomitant medications taken by participant including no treatment medication for type 1 diabetes mellitus (reported previously), event onset date was date event met seriousness criteria (reported previously) and details about participant’s diabetes mellitus/blood sugar level in relation to the event.

Company Comment:

The investigator assessed the Staphylococcal bacteraemia as not related to the blinded study drug VIR-7831 vs VIR-7832 vs Placebo.

The event is confounded by the participant's medical history of relatively poorly controlled type 1 diabetes mellitus 3 months prior to event, which may be associated with increased risk of infections, including Staphylococcus aureus bacteremia. The participant additionally did not receive treatment for type 1 diabetes mellitus. The SAE of Staphylococcal bacteraemia was assessed as not related to VIR-7831 or VIR-7832 or Placebo.

The Staphylococcal bacteraemia was assessed as Unexpected for VIR-7831 vs VIR-7832 vs Placebo as per the current Investigator's Brochure.

The information provided in this individual case does not warrant a change to the Investigator's Brochure and does not constitute an unanticipated problem or urgent safety measure at this time. This topic will continue to be monitored closely.

DATA SOURCE TABLES AND FIGURES

MODULAR APPENDICES PROVIDED FOR 215337

STUDY INFORMATION - ICH SPECIFIED APPENDICES ***Required for all 3 CPSR/CSR formats:***
Protocol and Protocol Amendments
Reporting and Analysis Plan
Sample Case Report Form
List of Investigators and Independent Ethics Committees (IECs)/ Institutional Review Boards (IRBs) (plus the name of the committee chair, if available).
Sponsor's and Investigator's Signatures
Publications based on the study.

STUDY INFORMATION - ICH SPECIFIED APPENDICES ***Required for the Full and Abbreviated CSRs/CPSRs:***
Sample Consent Forms
Brief CVs/Biographies
Study Administrative Table
STUDY INFORMATION - ICH SPECIFIED APPENDICES ***Required for the Full CPSR/CSR:***
Listing(s) of participants receiving study intervention(s) from specific batches, if more than one batch was used
Randomization scheme and codes
Audit Certificates
Statistical methods (technical data analysis appendix)
Documentation of inter-laboratory standardization methods and quality assurance procedures (if used)
Important publications referenced in the report.
STUDY INFORMATION - OTHER APPENDICES ***Required for the Full CPSR/CSR (if applicable):***
Bioanalytical methods and results
Certificates of Analysis
PK or population pk report
Biomarker report
Virology genotypic and phenotypic results
PGx Results
Health Outcomes report on direct cost data
Independent Data Monitoring Committee (IDMC)
DATA LISTINGS ***Required for all 3 CPSR/CSR formats:***
Adverse event listings (each participant)
Listing of individual laboratory measurements by participant
Country-specific participant Listings

DATA LISTINGS ***Required for the Full and Abbreviated CPSR/CSR:***
Discontinued/withdrawn participants
Protocol deviations
Participants excluded from the efficacy analysis
Demographic data
Concomitant medications
Compliance and/or drug concentration data (if available)
Individual efficacy response data
Other data listings

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Notary Events	Signature	Timestamp

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Completed	Security Checked	21 February 2024 | 17:26

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