20 May 2021
EMA/304600/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

GlaxoSmithKline use of sotrovimab (VIR-7831/GSK4182136) for the treatment of COVID-19

INN/active substance: sotrovimab

Procedure number: EMEA/H/A-5(3)/1508

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus is the causative agent of coronavirus disease 2019 (COVID-19). Early treatment of patients with confirmed COVID-19 presenting only mild symptoms can reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to ICU.

The European Medicines Agency (EMA) is aware of several therapeutic candidates with putative antiviral action which are currently in development for the treatment of these patients.

Amongst those treatments, sotrovimab (VIR-7831/GSK4182136), an investigational dual-action SARS-CoV-2 monoclonal antibody, has been associated with an 85% reduction in hospitalisation or death. Sotrovimab (VIR-7831/GSK4182136) has been evaluated against placebo in a phase 3 trial (COMET-ICE) as monotherapy for the early treatment of COVID-19 in adults at high risk of hospitalisation.

The Phase 3 portion of the COMET-ICE trial assessed the safety and efficacy of a single intravenous infusion of VIR-7831 (500 mg) or placebo in non-hospitalised participants globally. The interim analysis included 291 patients in the treatment arm and 292 patients in the placebo arm. The primary efficacy endpoint is the proportion of patients who have progression of COVID-19 as defined by the need for hospitalisation for at least 24 hours or death within 29 days of randomisation. Interim analysis of data from the 583 patients enrolled in the COMET-ICE trial, demonstrated an 85% (p=0.002) reduction in hospitalisation or death in patients receiving VIR-7831 as monotherapy compared to placebo[1].

These results are of great relevance and their application in the clinical setting before a formal authorisation is considered important in view of the current pandemic situation. In that respect, there is public health interest to seek a harmonised scientific opinion at EU level on currently available information on sotrovimab (VIR-7831/GSK4182136) and on potential conditions of use with a view to supporting national decisions.

On 14 April 2021 the European Medicines Agency Executive Director therefore triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the CHMP to give a scientific opinion on the currently available quality, preclinical and clinical data on the potential use of sotrovimab (VIR-7831/GSK4182136) for the treatment of patients with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at high risk of progressing to severe COVID-19.

2. Scientific discussion

2.1. Introduction

Sotrovimab (VIR-7831/GSK4182136) is a human neutralising anti-SARS-CoV-2 antibody, which contains a 2 amino acid Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. VIR-7831 binds to a conserved epitope in the SARS-CoV-2 receptor-binding domain (RBD), outside of the receptor-binding motif (RBM).

Binding to this highly conserved region creates a high barrier to resistant variant selection in vitro and allows VIR-7831 to retain activity in vitro against SARS-CoV-2 mutants.

Additionally, because VIR-7831 binds to a non-RBM epitope, VIR-7831 has a predictably orthogonal resistance profile to RBM-binding COVID-19 antibodies. Published epitope data for RBM-binding antibodies indicates a low likelihood of steric clash with VIR-7831. Thus, when combined with RBM-binding antibodies, VIR-7831 has the potential to increase the barrier to resistance to COVID-19 as

[1] https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-announce-vir-7831-reduces-hospitalisation-and-risk-of-death-in-early-treatment-of-adults-with-covid-19/

well as enhance the breadth of coverage of RBM-binding antibodies. The Fc domain of VIR-7831 includes a LS modification that extends antibody half-life and is also expected to enhance distribution to the respiratory mucosa. The LS modification does not impact wild-type Fc-mediated effector functions and VIR-7831 demonstrates activity in two key indirect antiviral mechanisms in vitro, ADCC and ADCP, which may also contribute to clinical effectiveness.

VIR-7831 is currently being investigated in several trials, of which the COMET-ICE is the pivotal study, for the following indication:

For the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19.

VIR-7831 has been evaluated for the treatment of non-hospitalised subjects and showed a risk reduction of hospitalisation or death of 85% (p=0.002) in the first interim analysis. VIR-7831 is currently being evaluated in other phase 3 studies including another study of non-hospitalised patients, which also includes treatment with intramuscular administration, a study in hospitalised patients and a study in non-hospitalised patients using combination therapy with another monoclonal antibody.

The CHMP assessed the currently available quality, preclinical and clinical data.

2.2. Clinical aspects

VIR-7831-5001 (214367, also known as COMET-ICE) is the only pivotal study supporting this procedure. Available safety data from the ongoing COMET-PEAK (Part-A), ACTIV-3-TICO and BLAZE-4 study are included as supporting information.

COMET-ICE (NCT04545060): A randomised, double-blind, placebo-controlled study to assess the safety and efficacy of VIR-7831 in adults with confirmed COVID 19 (mild, early disease with less than 5 days of symptoms) at risk of disease progression (recruitment closed/ongoing).

COMET-PEAK (NCT04779879): A multicentre, randomised, parallel group study to characterise the safety, tolerability, and pharmacokinetics of a single intravenous dose of a second generation VIR-7831 in non-hospitalised participants with mild-to-moderate COVID-19. The study has two parts. Part A is double-blind and will evaluate VIR-7831 Gen2 and Gen1 administered via intravenous (IV) infusion. Part B will be open- label and compare Gen2 administered via IV infusion and intramuscular (IM) injection (ongoing).

ACTIV-3-TICO (NCT04501978): A platform study in hospitalised participants sponsored by NIAID and NIH – an adaptive, randomised, blinded, controlled trial of the safety and efficacy of investigational therapeutics for hospitalised participants who have had COVID-19 symptoms for ≤12 days, with or without end-stage organ dysfunction or failure. On 01 March 2021, the Data and Safety Monitoring Board (DSMB) recommended recruitment in the VIR-7831 subprotocol should cease, and follow-up of participants already randomised is ongoing.

BLAZE-4 (NCT04634409): A randomised, double-blind, placebo-controlled, phase II study to evaluate the efficacy and safety of mono and combination therapy with monoclonal antibodies in participants with mild-to-moderate COVID-19. VIR-7831 is included in treatment arm 7 with bamlanivimab; arm 8, a placebo arm, was randomised concurrently with arm 7. There is no monotherapy group evaluating VIR- 7831 alone in the study. The study is sponsored and conducted by Eli Lilly (ongoing).

Table 1 - Overview of key efficacy data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication 1					
COMET-ICE Randomised, double-blind, multi centre, placebo-controlled trial of VIR-7831 against SARS-CoV-2 for the prevention of progression of mild/moderate COVID-19, with interim monitoring to allow early stopping for futility, efficacy or safety. Study ID: 214367 Ref: overview and protocol provided by the Applicant	Primary objective Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19 Primary endpoint: Proportion of participants who have progression of COVID-19 through Day 29 as defined by: - Hospitalisation >24 hours for acute management of illness OR -Death	Adults with confirmed COVID-19 (mild/moderate, early disease with ≤5 days symptoms) at risk of disease progression n=1360 participants (680 per treatment arm) planned	Main inclusion criteria: Age: ≤ 18 years with one or more of the following risk factors: diabetes, obesity (BMI>35), chronic kidney disease, congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease, and moderate to severe asthma OR Participant ≥ 55 years old, irrespective of co-morbidities. Positive SARS-CoV-2 test result (by any validated diagnostic test e.g. RT-PCR, antigen-based testing on any specimen type) AND Oxygen saturation ≥94% on room air AND COVID-19 defined by one or more of the following symptoms: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhea, shortness of breath on exertion AND	Randomised 1:1 to receive a single, IV dose of VIR-7831 (500 mg) Gen 1 or placebo, administered over 60 minutes	Results are based on the first interim analysis. 292 subjects were included in the placebo arm and 291 subjects were included in the VIR-7831 arm. 21 (7%) subjects in the placebo arm and 3 (1%) subjects in the VIR-7831 arm met the primary endpoint. The adjusted relative risk ratio with 97.24% CI was 0.15 (0.04;0.56), which indicates an 85% reduction in the risk of COVID-19 progression to hospitalisation >24 hours for acute management of illness or death due to any cause through Day

			Less than or equal to 5 days from onset of symptoms Main exclusion criteria: Currently hospitalized or judged by the investigator as likely to require hospitalisation in the next 24 hours Symptoms consistent with severe COVID-19 as defined by shortness of breath at rest or respiratory distress or requiring supplemental oxygen. Receipt of any vaccine within 48 hours prior to enrolment. Receipt of a SARs-CoV-2 vaccine prior to randomisation at any timepoint. Vaccination (including vaccination for SARS-CoV-2) will not be allowed for 4 weeks after dosing. Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within the last 3 months.		29 with VIR-7831.

2.2.1. Clinical pharmacology

Pharmacokinetics

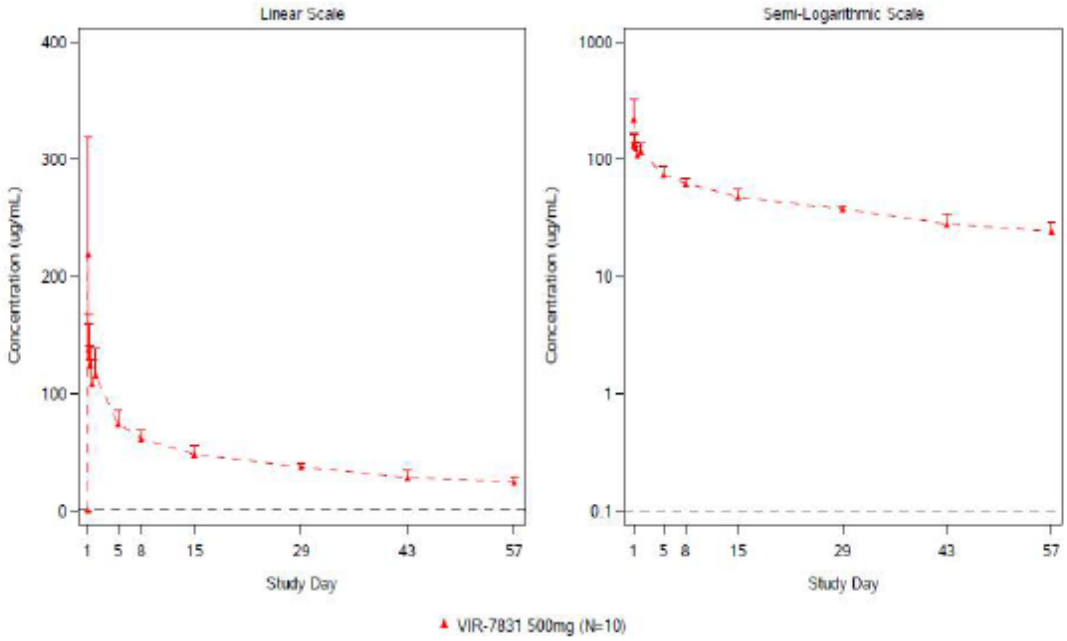
No Phase 1 studies were conducted. The applicant proceeded directly to studies in patients infected with SARS-CoV-2. Hence no absorption, distribution and elimination studies have been conducted. Since the product is a human IgG1 monoclonal antibody, several assumptions were made about its likely pharmacokinetics in line with publicly available data on similar products that have been modified to prolong the serum half-life.

Some pharmacokinetic (PK) data were obtained from the COMET-ICE trial. These data were also used in support of the recommended single 500 mg dose.

At present, there are some serum PK through Day 57 from 10 patients in the Lead-in phase of the study. One patient discontinued early due to withdrawal of consent following infusion with VIR-7831. PK sampling will continue for 6 months for all patients to document half-life.

PK parameters for VIR-7831 based on actual times and the preliminary mean PK profile are presented in Figure 1 and Table 2, respectively. The mean maximum concentration (Cmax) of 500 mg VIR-7831 was 219 µg/mL following a 1-hour IV infusion. The mean serum level on Day 29 is 37.2 µg/mL.

Figure 1 – Preliminary mean (+SD) VIR-7831 serum concentration-time plots (linear and semi-log): Lead-in



Note: LLQ=0.1 µg/mL. Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist.
Data is based on 1-hour infusion time.

Table 2 – Preliminary VIR-7831 PK parameters following a 500 mg IV dose

Parameter	Dose 500 mg (N = 9[a])
C_{max}, µg/mL	219 (99.6)
T_{max}, day	0.042 (0.04, 0.05)
C_{last}, µg/mL	24.1 (4.8)
T_{last}, day	53.6 (51.7, 59.9)
C_{D29}, µg/mL	37.2 (2.9)
AUC_{D1-29}, day*µg/mL	1529 (147.3)
AUC_{last}, day*µg/mL	2275 (201.1)
AUC % Extrapolated	38.4 (11.3)
AUC_{inf}, day*µg/mL	TBD[b]
CL (mL/day)	TBD[b]
V_z, L	TBD[b]
$t_{1/2}$, day	TBD[b]

Parameters are reported as mean (SD) except for T_{max}, T_{last} and $t_{1/2}$, which are presented as median (min, max).
Data is based on 1-hour infusion time.
[a] N=9 for C_{max}, T_{max}, C_{last}, T_{last}, C_{D29}, N=8 for AUC_{D1-29}, AUC_{last}, AUC % Extrapolated.
[b] Final summary statistics for AUC_{inf}, as well as CL,V and $t_{1/2}$ will be reported when sufficient data are available so that ≤20% of the AUC_{inf} is extrapolated observation range for λ_z spans > 2 half-lives.

Partial sparse serum PK through study Day 29 from 176 participants in the Expansion phase of COMET-ICE is also available.

The mean serum concentration of VIR-7831 on study Day 29 from 69 participants is 34.6 µg/mL (range: 17-54 µg/mL). Overall, Day 29 serum concentrations had low variability (22.2% CV; mean: 34.9 µg/mL; SD: 7.8.), irrespective of potential intrinsic factors.

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

Pharmacokinetics in special populations

The information regarding PK of VIR-7831 in special populations is limited.

Elderly patients

Of the 430 participants on VIR-7831 treatment in COMET-ICE, 20% were aged 65 years and older and 10% were over 70 years of age. Hence, data in elderly is limited, and differences in PK between younger and elderly has not been evaluated. However, no particular theoretical concern has been identified. Use in elderly is acceptable and a dose adjustment is not considered necessary.

[2] Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? MAbs. 2011 Jan-Feb;3(1):61-6. doi: 10.4161/mabs.3.1.13799. Epub 2011 Jan 1. PMID: 20962582; PMCID: PMC3038012.

Paediatric patients

VIR-7831 is not intended for use in patients younger than 12 years or adolescents weighing less than 40 kg. The safety and effectiveness of VIR-7831 have not been assessed in paediatric patients. Assuming conventional allometric scaling of exposure with bodyweight, and NHANES data, the overlap in exposure between adults and adolescents (>12 years and >40 kg) is 67% (60% without the weight constraint). VIR-7831 exposure is expected to be marginally above that in adults so the risk of under-dosing with a 500 mg dose is small. Furthermore, the range of body weight for adults treated in COMET-ICE was 36-165 kg. Therefore, no dose adjustment has been proposed for adolescents of 40 kg+ body weight.

Patients with renal impairment

No clinical trials have been conducted to evaluate the PK of VIR-7831 in patients with renal impairment. Based on experience with other mAbs, renal impairment and dialysis are not expected to impact the PK of VIR-7831. The impact of other covariates (e.g. sex, race, body weight, BMI, disease severity, hepatic impairment) on the PK of VIR-7831 is unknown. Since VIR-7831 is not renally excreted or metabolised by cytochrome P450 enzymes, interactions with concomitant medications that are renally excreted or that are substrates, inducers or inhibitors of cytochrome P450 enzymes are unlikely. Similarly, dialysis is not expected to impact the PK of VIR-7831.

Mechanism of action

Sotrovimab (VIR-7831/GSK4182136) is a human neutralising anti-SARS-CoV-2 antibody, which contains a 2 amino acid Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. VIR-7831 binds to a conserved epitope in the SARS-CoV-2 receptor-binding domain (RBD), outside of the receptor-binding motif (RBM) where the majority of other COVID-19 monoclonal antibodies in development bind.

Binding to this highly conserved region creates a high barrier to resistant variant selection in vitro and allows VIR-7831 to retain activity in vitro against wild-type SARS-CoV-2 mutants. VIR-7831 neutralises SARS-CoV-2 live virus and pseudotyped virus in vitro and retains activity against the UK (B.1.1.7), South Africa (B.1.351), Brazil (P.1) and California (CAL.20C) variant pseudotyped viruses. Additionally, VIR-7831 can mediate two key indirect antiviral mechanisms, antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) in vitro, which may also contribute to its clinical effectiveness.

Because VIR-7831 binds to a non-RBM epitope, VIR-7831 has a predictably orthogonal resistance profile to RBM-binding COVID-19 antibodies. Published epitope data for RBM-binding antibodies indicates a low likelihood of steric clash with VIR-7831.

Rationale for Dosing Recommendations

The dosing regimen for VIR-7831 is a single 500 mg dose for intravenous (IV) infusion over 30 minutes. This is also the only dose used in the COMET-ICE study and the infusion duration in the BLAZE-4 study.

VIR-7831 neutralised SARS-CoV-2 live virus with an average EC_{90} value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL). A 500 mg IV dose has been selected since it is expected to ensure that VIR-7831 concentrations in lung are maintained at or above levels anticipated to be neutralising for the first 28 days after administration. As reported above, the mean Day 29 serum concentration in COMET-ICE patients with available data was 34.9 µg/mL (95% CI: 33.2, 36.7). Based on this result, one 500 mg IV dose of VIR-7831 is expected to maintain serum levels at or above 25x lung-tissue adjusted EC_{90} for 28 days in 50% of patients and at or above 15x lung-tissue adjusted EC_{90} for 28 days in 97.5% of

patients. These estimates are based on the upper range value for EC_{90} (0.33 µg/mL) and an assumed lung:serum ratio for IgG of 0.25, derived from published data giving a range from 0.25-0.68 for whole lung. Based on an 85% reduction in the proportion with progression to >24 hours hospitalisation or death through Day 29 and on the mean serum concentration on Day 29 (34.9 µg/mL), a 500 mg dose is expected to achieve supratherapeutic levels in plasma and pulmonary tissues and therapeutic levels in nasal tissues. Also, the 500 mg dose is predicted to maintain lung concentrations that provide protection against P337H and P337T variants, which confer 5-8-fold shifts in EC_{90} in pseudotyped virus assays.

2.2.2. Data on efficacy

VIR-7831 is currently being investigated in several trials of which the COMET-ICE is the pivotal study for the current Art 5(3) procedure for the following indication:

For the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19.

Efficacy data from other supportive studies are not yet available.

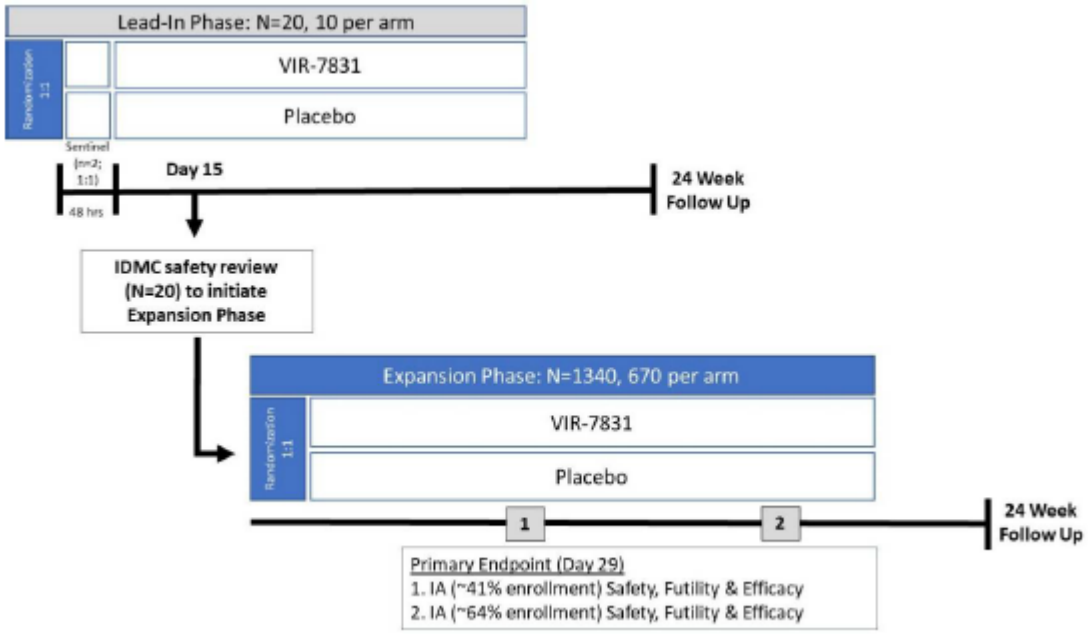
COMET-ICE was initiated in August 2020 as a seamless First in Human (FIH), Phase 2/3 study evaluating treatment of mild/moderate COVID-19 in adults at risk of disease progression. There was a FIH lead-in phase and an Expansion phase.

Methods

COMET-ICE is a randomised, double-blind, multi-centre, placebo-controlled study to assess the safety and efficacy of mAb VIR-7831 for the early treatment of COVID-19 in non-hospitalised participants who are at risk of disease progression, including but not limited to older adults (age ≥55 years) and all individuals aged 18 or older with specific comorbidities, including diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate-to-severe asthma.

The study comprises two phases: a lead-in phase and an expansion phase (Figure 2).

Figure 2 – Study design schematic



The Lead-In phase included 21 non-hospitalised participants who have early, mild/moderate COVID-19 and are at high risk of disease progression. An independent data monitoring committee met to review unblinded safety data after 20 participants from lead-in cohort completed Day 15 (DCO: 28 September 2020). One participant discontinued early due to withdrawal of consent following infusion with VIR-7831. The IDMC recommended the study to proceed with the Expansion-phase to enrol additional participants across each treatment arm (1340 participants in total).

Study population:

Eligible patients were to be non-hospitalised:

- Adults aged ≥55 years regardless of any comorbidities allowed (target 15% >70 years) OR
- Adults aged <55 years who had at least one of diabetes requiring medication, obesity (BMI>35), chronic kidney disease (eGFR MDRD <60), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease or moderate-to-severe asthma.

They were also required to have:

- A positive SARS-CoV-2 test result by any validated diagnostic test (e.g. RT-PCR, antigen-based testing on any specimen type) and from any respiratory specimen collected ≤ 7 days prior to study entry. Any patient with a negative test prior to screening but a positive test obtained at screening was eligible if symptom onset was within ≤ 5 days.

AND

- Oxygen saturation ≥94% on room air

AND

- 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

AND to be enrolled when

- ≤ 5 days from symptom onset

Patients were excluded if they were/had:

- Hospitalised or judged by the investigator as likely to require hospitalisation within 24 hours
- Symptoms consistent with severe COVID-19 as defined by shortness of breath at rest or respiratory distress or requiring supplemental oxygen.
- Judged likely to die in the next 7 days.
- Severely immunocompromised, including but not limited to cancer actively receiving immunosuppressive chemotherapy or immunotherapy, solid organ transplant or allogeneic stem cell transplant within the last 3 months or requiring systemic corticosteroids equivalent to ≥ 0.5 mg/kg of body weight per day of prednisone within 6 weeks of randomisation
- Known hypersensitivity to any constituent present in the investigational product
- A history of anaphylaxis or hypersensitivity to a monoclonal antibody

They were not to have received COVID-19 vaccine at any time or any vaccine within 48 hours of enrolment or convalescent plasma within 3 months of enrolment.

Randomisation, blinding and treatment

Eligible patients were randomised 1:1 using IWRS to receive a single IV infusion of either VIR-7831 (500 mg) or equal volume (20 mL) saline placebo over 1 hour. The study pharmacist prepared the infusions so that all other study site staff and patients were unaware of the treatment assignment. In the Lead-in phase randomisation was stratified by age (≤70 or >70 years) and by symptom duration prior to enrolment (≤3 days or 4-5 days). In the Expansion phase, randomisation was stratified by age (≤70 or >70 years), symptom duration prior to enrolment (≤3 days or 4-5 days) and region (N. America, S. America, Europe, Asia, ROW).

Patients could receive all locally applicable standard of care for acute COVID-19 excluding receipt of hydroxychloroquine, chloroquine, convalescent plasma or other anti-SARS-CoV-2 mAb.

During the Expansion phase, patients were to be called by the study site once daily, except on in-clinic visit days, for 14 days post-infusion to monitor for progression of disease. Patients were questioned on any dyspnoea at rest or severe dyspnoea on exertion, haemoptysis, cyanosis or mental status changes. If any of these was reported, patients were directed to seek medical attention. In addition, any healthcare encounters or new concomitant medications were recorded. After Day 29, patients were to be called every 4 weeks through Week 20 to detect any recurrence of COVID-19 or any illness that resulted in healthcare encounters. Any medications as a result of illness were to be recorded.

Objectives and endpoints

Primary and main secondary efficacy objectives and endpoints are provided in the following table.

Objectives	Endpoints
Primary	
• Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19	• Proportion of participants who have progression of COVID-19 through Day 29 as defined by: 1. Hospitalization > 24 hours for acute management of illness OR 2. Death
Secondary	
Efficacy • Evaluate the efficacy of VIR-7831 versus placebo in preventing the progression of mild/moderate COVID-19	Proportion of participants who have progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR • Hospitalization for acute management of illness OR • Death
• Evaluate the impact of VIR-7831 versus placebo on the duration and the severity of COVID-19 clinical symptoms	• Mean change in FLU-PRO Plus total score comparing Vir-7831 vs. Placebo (AUC through Day 7) • Time to symptom alleviation using the FLU-PRO Plus
• Evaluate the efficacy of VIR-7831 versus placebo in reducing SARS-CoV-2 viral load	• Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8
• Evaluate the efficacy of VIR-7831 against versus placebo in preventing COVID-19 respiratory disease progression	• Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifest by requirement for and method of supplemental oxygen at Day 8, Day 15, Day 22, or Day 29
• Evaluate the efficacy of VIR-7831 versus placebo in preventing mortality	• 29-day, 60-day, and 90-day all cause mortality

Sample size calculation

The expected sample size was 680 patients per arm with no sample size re-estimation planned.

Thus, up to 1360 (680 per arm) were to be randomised to provide approximately 90% power to detect

a 37.5% relative efficacy in reducing progression of COVID-19 through Day 29 at the overall two-sided 5% significance level with assumed progression of COVID-19 rates of 16% in the placebo arm and 10% in the VIR-7831 arm, respectively. The minimal detectable efficacy for this design at the final efficacy analysis was approximately 25% if the disease progression rates was 16% in the placebo arm.

Statistical approach

The primary endpoint (reduction in the rate of hospitalisation over 24 hours for acute management of any illness or death due to any cause through day 29; see above) was selected prior to protocol finalisation. This final primary endpoint replaced the primary endpoint previously agreed in CHMP scientific advice, which was the proportion that developed hypoxaemia [O_2 saturation <94% on room air on two occasions at least 8 hours apart] OR hospitalisation requiring non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, ECMO OR death during the 28-day follow-up period. At the time of follow-up scientific advice, at which time the applicant proposed the replacement primary endpoint, the CHMP recommended adherence to the prior agreed primary endpoint.

The study was planned with a group sequential design with two interim analyses, each of which could assess futility or success. A Lan-DeMets alpha-spending function to control the type I error was to be used, using a Pocock analogue rule for futility and a Hwang-Shih-DeCani (with parameter $\gamma = 1$) analogue for efficacy.

- The First Interim Analysis (IA1) was to occur when ~41% of patients had reached Day 29
- The Second Interim Analysis (IA2) was to occur when ~64% of patients had reached Day 29

Interim analyses were to be performed by an independent Statistics Data Analysis Centre and reviewed by an IDMC, who could recommend stopping for futility or for success. The decision criteria were to be defined in the IDMC charter and were also listed in the statistical analysis plan (see criteria below).

The pre-defined analysis populations were defined as shown below.

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

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

A separate statistical analysis plan (SAP) was developed (dated 29 January 2021) which provides some additional details.

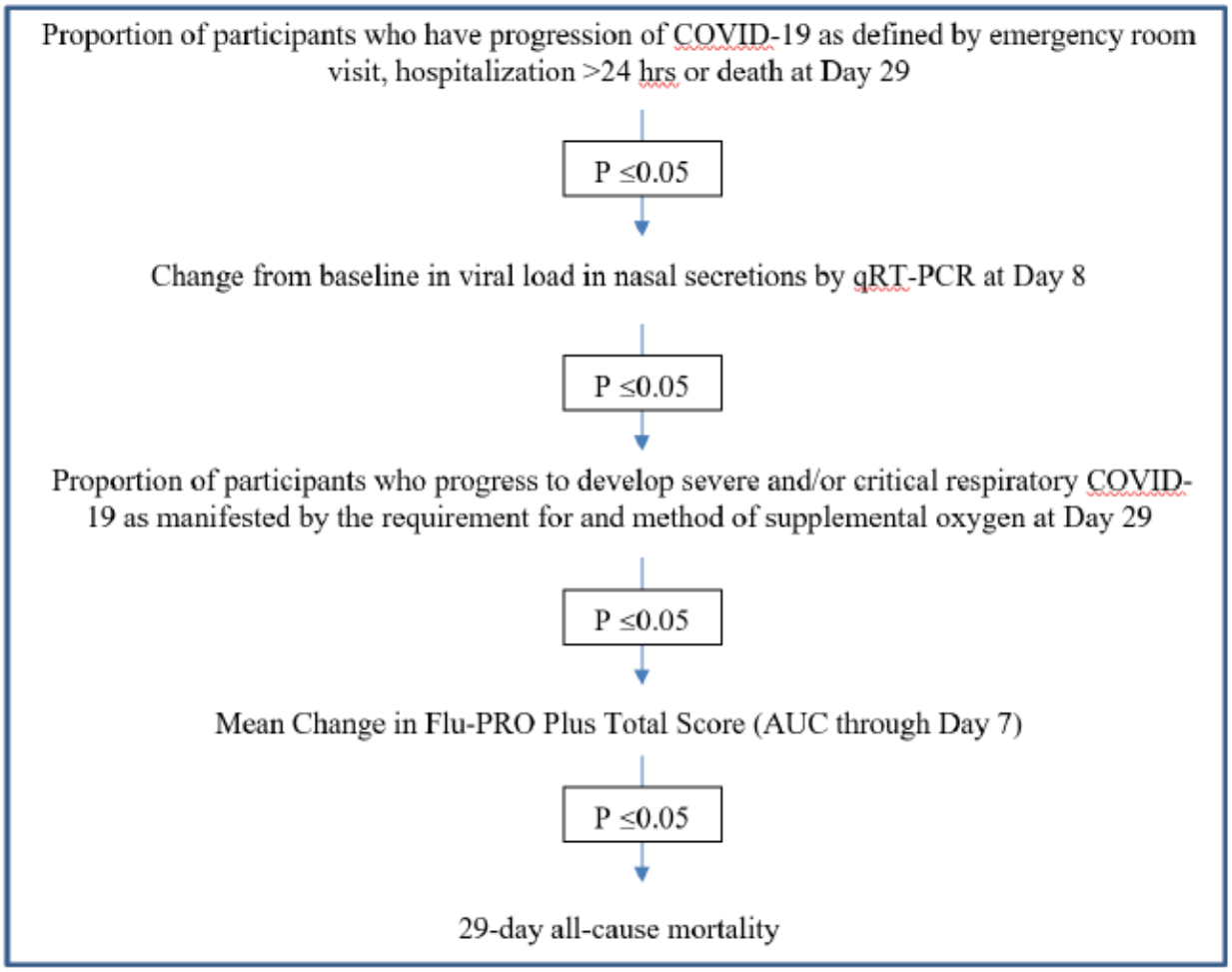
As indicated above, the ITT Analysis Set was to be used for the primary and secondary efficacy analyses. In the case of a difference between the stratification assigned at the time of randomisation and the data collected in the eCRF, the analyses were to be performed using the data collected in the eCRF. All analyses were to be adjusted for duration of symptoms (≤3 days vs. 4-5 days), age (≤70 vs. >70 years old) and region (North America, South America, Europe, Asia, RoW). Although not a stratification factor at randomisation, the SAP states that analyses were also adjusted for gender.

Windows were set around the data considered for each study visit.

The primary endpoint was to be summarised using counts and proportions of the number of patients with progression of COVID-19 and analysed using a log-binomial regression model adjusting for duration of symptoms, age, region and gender (as above). The relative risk of progression was to be calculated from the log-binomial generalised linear model.

At each of the interim and final efficacy analysis, appropriate CI based on the adjusted significance level were to be provided. For example, if the remaining alpha for the final analysis is 0.024, 97.6% CI will be provided for the final efficacy analysis.

Secondary endpoints were to be formally analysed at the final Day 29 analysis and tested with alpha level of 5% (two-sided). The testing of secondary endpoints was adjusted for multiplicity by using the following hierarchy:



The SAP also gives details of intercurrent events and approaches to handling missing data. In general, unless otherwise specified, the handling strategy for all identified intercurrent events was to be based on a treatment policy approach; specifically, the effects estimated were to be based on initial randomised treatment arm regardless of whether the patient had experienced an intercurrent event. If possible, data was to continue to be collected after the occurrence of the intercurrent event, until the patient either completed the study or withdrew from the study before completion.

Missing data could occur due to study withdrawal or patients lost to follow-up before the completion of the study or due to intermittent missing values (i.e. data between two non-missing assessments). For all endpoints, missing data were to be imputed under a missing at random (MAR) assumption using a multiple imputation (MI) model. The MI model was to include covariates: treatment, duration of symptoms (≤3 days vs. 4-5 days), age group (≤70 vs. >70 years old), region (North America, South America, Europe, Asia and RoW), gender (male, female) and baseline of the variable of interest (if appropriate).

A tipping point analyses was to be performed for the primary endpoint as a missing data sensitivity analysis. The underlying response rate among those subjects with missing response status in each arm

was to be tested ranging between 0 and 1. This analysis was to be two-dimensional, i.e. allowing for assumptions about the assumed response rate (and thus missing outcomes) in the two arms to vary independently, including scenarios where dropouts on VIR-7831 have worse outcomes than dropouts on placebo. For combinations of the assumed response rates in the two arms, the number of additional responders among subjects with missing response was to be imputed multiple times by drawing from a binomial distribution. The risk ratio and associated standard error for each imputed dataset was to be calculated and results combined using Rubin's rules to calculate the test statistic and the corresponding p-value. Results were to be presented via a heatmap.

Results for a composite estimand, where study withdrawals were treated as having progressed, were to be presented as supplementary analyses.

Decision criteria

Futility due to lack of efficacy and study success due to overwhelming benefit were to be formally assessed as described above for IA1 and IA2 based on data collected up to 29 days after treatment from ~280/arm in IA1 and ~435/arm in IA2. Study stopping criteria were defined using group sequential design methodology, using an alpha-spending function to control the type I error.

The table below shows the stopping boundaries based on p-values (one-sided) from the planned interim analysis and on the Z score scale. The p-values or Z scores at each interim analysis were to be plotted against the boundaries and if either the futility or efficacy success boundary was crossed the IDMC was to recommended stopping the study.

The boundaries shown were based on the estimated amount of information at each interim. The actual boundaries could be re-determined based on the exact amount of information at the time of the interim analyses. Boundaries were to be determined using PASS 2019, using the group sequential tests for two proportions (simulation procedure) with the following criteria: 2-sided overall 5% significance level (symmetric), equal allocation, 3 planned stages at actual and planned (future) information proportions (minimum 5 decimal places), no continuity correction, 0.1 zero count adjustment added to zero cells only and non-binding futility boundaries and hold-out efficacy boundaries.

Table 3 – Planned formal stopping rules for efficacy success and efficacy futility

Stage/Formal Analysis	Target Sample Size to D29	Efficacy Success Boundaries				Efficacy Futility Boundaries			
		p-value		Z-Score		p-value		Z-score	
		Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
1	560	<0.01335	<0.01335	-2.2159	2.2159	>0.21147	>0.21147	-0.8013	0.8013
2	870	<0.00973	<0.00973	-2.3367	2.3367	>0.09363	>0.09363	-1.3187	1.3187
Final (D29)	1360	<0.01103	<0.01103	-2.2894	2.2894	>0.01103	>0.01103	-2.2894	2.2894

The IDMC was charged with conducting unblinded safety reviews when data to at least Day 15 were available from pre-defined enrolment targets, these being 60 initially and then, if considered necessary, 100 patients.

Lead-in phase and decision to progress to Expansion Phase

During the Lead-In phase, randomisation was stratified by age (</> 70 years) and symptom duration (up to 3 vs. 4-5 days). Patients were admitted to a study unit for 7 days. If there were no signs and symptoms of progression after 7 days, they were discharged and contacted daily by telephone as described above in the Expansion phase.

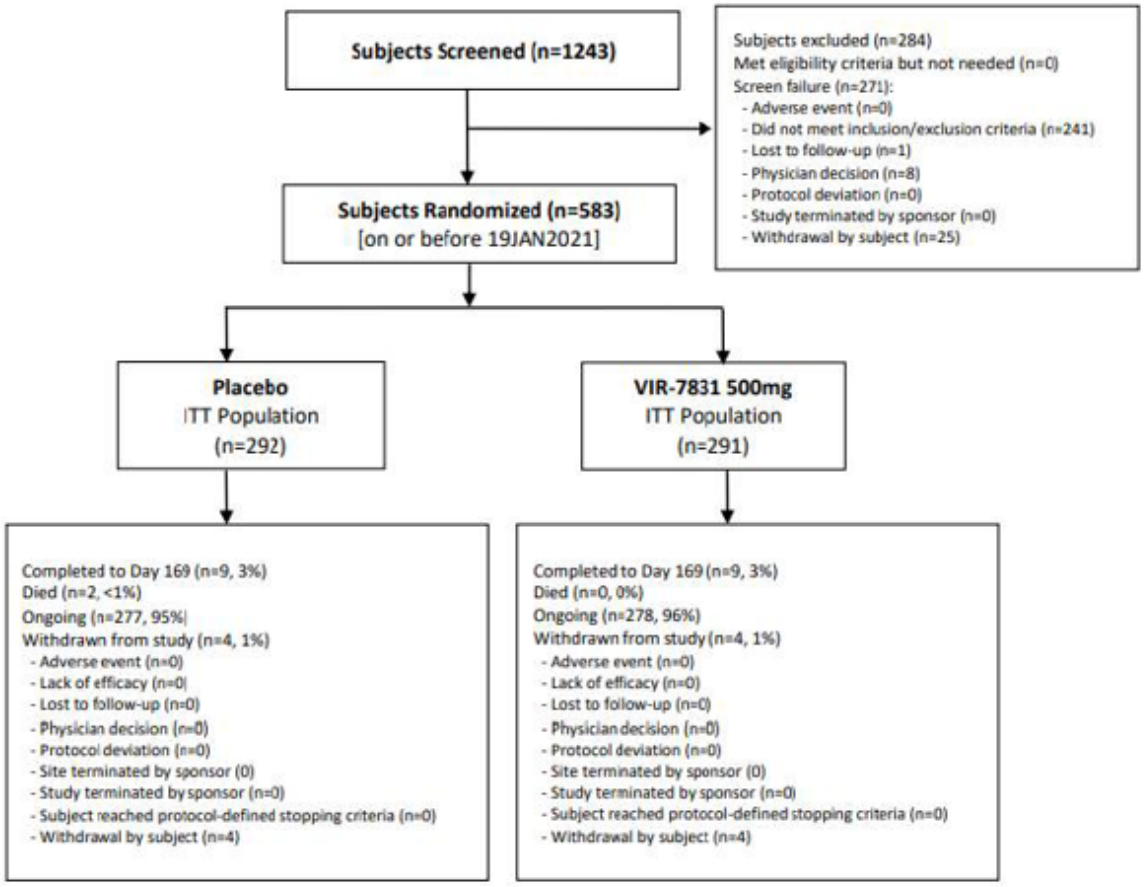
The Lead-in phase enrolled 21 patients. The independent data monitoring committee met to review unblinded safety data after 20 patients from lead-in cohort completed Day 15 (cut-off date 28 September 2020). One patient had discontinued early due to withdrawal of consent following infusion with VIR-7831. The IDMC recommended the study to proceed with the Expansion phase to enrol up to 1340 patients.

All available clinical efficacy data comes from the first interim analysis of the COMET-ICE study.

A total of 583 participants (ITT [IA]) were randomly assigned to study treatment (VIR-7831: 291; placebo: 292) by 19 January 2021 and therefore had an opportunity to be followed to Day 29 and data cleaned by the first interim analysis data cut-off (04 March 2021). Participants were recruited from sites in the US (92%), Canada (7%), Spain (<1%) and Brazil (<1%).

Participant flow is shown in Figure 3.

Figure 3 – Participant disposition through day 29 (enrolled) (ITT[IA])



Interim Analysis 1 DCO: 04 March 2021.

Note: Participants randomised treatment regardless of whether infusion was given. One participant in the placebo group and 3 in the VIR-7831 500 mg group withdrew consent prior to treatment infusion.

Demographics and baseline characteristics

Two patients at one site were unblinded by the pharmacist during the study. The investigator and patients remained blinded. These patients did not progress at the IA1 DCO.

Recruitment continued between the IA1 DCO (04 March 2021) and the IDMC recommendation to halt enrolment.

The baseline demographic and disease characteristics were well balanced between treatment arms (Table 4). Overall, 54% were female. The median age was 53 years (range: 18-96) and 22% were aged 65 years or older with 11% aged > 70 years.

Table 4 – Summary of demographics characteristics at baseline (ITT [IA])

Parameter	Placebo (N=292)	VIR-7831 500 mg (N=291)	Total (N=583)
Sex			
Male	131 (45%)	135 (46%)	266 (46%)
Female	161 (55%)	156 (54%)	317 (54%)
Age (Years)[a]			
Mean (SD)	52.5 (15.24)	51.6 (15.18)	52.0 (15.21)
Median (Min, Max)	52.5 (18, 88)	53 (18,96)	53 (18,96)
Age Group (Years)			
≤18	3 (1%)	1 (<1%)	4 (<1%)
19 to 64	224 (77%)	227 (78%)	451 (77%)
≥65	65 (22%)	63 (22%)	128 (22%)
Age Group Strata (Years)			
≤70	260 (89%)	258 (89%)	518 (89%)
>70	32 (11%)	33 (11%)	65 (11%)
Ethnicity			
Hispanic or Latino	178 (61%)	190 (65%)	368 (63%)
Not Hispanic or Latino	141 (39%)	101 (35%)	215 (37%)
Race (high level)			
American Indian or Alaska Native	0	1 (<1%)	1 (<1%)
Asian	17 (6%)	17 (6%)	34 (6%)
Black or African American	22 (8%)	16 (6%)	38 (7%)
White	252 (87%)	254 (88%)	506 (87%)
Mixed Race	0	2 (<1)	2 (<1%)
Body Mass Index (BMI) (kg/m²)			
Mean (SD)	32.09 (6.26)	32.03 (6.36)	32.06 (6.30)
Median (Min, Max)	31.62 (20.0, 54.9)	31.70 (17.0, 60.5)	31.64 (17.0, 60.5)

Interim Analysis 1 DCO: 04 March 2021

a Age is imputed from year of birth. The calculation uses 30 June as the day and month and calculates age relative to Screening date.

At baseline, the majority of participants (88%) were confirmed positive for SARS-CoV-2 by a local RT-PCR test result, and the remainder (12%) by a positive antigen test result, and the proportions for each method were similar across both the treatment arms. Based on the preliminary data, baseline viral load was similar across treatment arms for all baseline viral load cut-off groups (Table 5).

Table 5 – Summary of SARS-CoV-2 test results at baseline (ITT [IA])

	Placebo (N=292)	VIR-7831 500mg (N=291)	Total (N=583)
Positive Local SARS-CoV2 Test Result[a]			
Yes	292 (100%)	291 (100%)	583 (100%)
Specimen Type[a]			
Nasopharyngeal Swab	192 (66%)	175 (60%)	367 (63%)
Nasal Cavity Swab	91 (31%)	100 (34%)	191 (33%)
Oropharyngeal Swab	3 (1%)	11 (4%)	14 (2%)
Saliva	6 (2%)	3 (1%)	9 (2%)
Other	0	2 (1%)	2 (<1%)
Method Diagnosis[a]			
RT-PCR	258 (88%)	253 (87%)	511 (88%)
Antigen	34 (12%)	38 (13%)	72 (12%)
Baseline SARS-CoV2 Viral Load (log10 copies/mL) in Nasal Secretions[b]			
n	179	162	341
Mean (SD)	6.643 (1.8569)	6.503 (1.7969)	6.576 (1.8273)
Median (Min, Max)	7.018 (3.047, 9.839)	6.638 (3.047,9.985)	6.835 (3.047, 9.985)
<Lower limit of quantification (<2228 copies/mL)	9 (5%)	8 (5%)	17 (5%)
$\leq 10^5$	33 (18%)	28 (17%)	61 (18%)
$>10^5 - \leq 10^6$	23 (13%)	29 (18%)	52 (15%)
$>10^6 - \leq 10^7$	24 (13%)	26 (16%)	50 (15%)
$>10^7$	90 (50%)	71 (44%)	161 (47%)

Interim Analysis 1 DCO: 04 March 2021

a. SARS-CoV-2 diagnostic test results reflects point-of-care or local laboratory test at Screening, and not Baseline viral load at Day 1.

b. Central Nasopharyngeal Swab. Percentages based on population with detectable SARS-CoV-2 test value at baseline in dataset available at IA1 DCO. Values less that the lower limit of quantification (LLQ=2228 copies/mL) have been imputed to 0.5xLLQ prior to taking the log 10 value.

The three most common pre-defined risk factors or comorbidities in both treatment groups were obesity, 55 years of age or older and diabetes requiring medication. The most common COVID-19-related symptoms at baseline are also presented.

Table 6 – Summary of disease characteristics at baseline (ITT [IA])

	Placebo (N=292)	VIR-7831 500mg (N=291)	Total (N=583)
Conditions as risk factor for COVID-19 progression[a]			
Obesity (BMI >30 kg/m²)	187 (64%)	182 (63%)	369 (63%)
>= 55 (Years)	141 (48%)	135 (46%)	276 (47%)
Diabetes requiring medication	66 (23%)	66 (23%)	132 (23%)
Moderate to severe asthma	46 (15%)	46 (16%)	92 (16%)
COPD	10 (3%)	14 (5%)	24 (4%)
Chronic kidney disease	4 (1%)	1 (<1%)	5 (<1%)
Congestive heart failure	3 (1%)	1 (<1%)	4 (<1%)
Number of conditions met			
0	2 (<1%)	0	2 (<1%)
1	168 (58%)	170 (58%)	338 (58%)
2	86 (29%)	91 (31%)	177 (30%)
3	27 (9%)	27 (9%)	54 (9%)
>3	9 (3%)	3 (1%)	12 (2%)
Symptoms present (PI reported)			
Cough	247 (85%)	240 (82%)	487 (84%)
Muscle Aches/Myalgia	215 (74%)	215 (74%)	430 (74%)
Headache	216 (74%)	202 (69%)	418 (72%)
Fatigue	183 (63%)	180 (62%)	363 (62%)
Malaise	172 (59%)	172 (59%)	344 (59%)
Sore Throat	172 (59%)	171 (59%)	343 (59%)
Fever	168 (58%)	164 (56%)	332 (57%)
Loss of Taste	159 (54%)	171 (59%)	307 (57%)
Chills	158 (54%)	164 (56%)	322 (55%)
Loss of Smell	152 (52%)	175 (60%)	327 (56%)
Joint Pain/Arthralgia	153 (52%)	153 (53%)	306 (52%)
Shortness of Breath	131 (45%)	131 (45%)	262 (45%)
Diarrhoea	101 (35%)	87 (30%)	188 (32%)
Nausea	91 (31%)	85 (29%)	176 (30%)
Vomiting	37 (13%)	34 (12%)	71 (12%)
Symptom duration (Days)			
≤3	171 (59%)	167 (57%)	338 (58%)
4-5	121 (41%)	123 (42%)	244 (42%)
>5	0	1 (<1%)	1 (<1%)

Interim Analysis 1 DCO: 04 March 2021

a. Medical Conditions present as risk factors at Screening for progression include: diabetes (requiring medication), obesity (BMI was amended under protocol amendment 1 from >30 to >35. Participants are only summarised in the BMI threshold under which they were screened.), chronic kidney disease (i.e., eGFR <60 by MDRD), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion), and moderate-to-severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

Note: Participants may occur more than once in the list of risk factors and the list of symptoms present.

Results

Primary endpoint analysis

Through Day 29, treatment with a single 500 mg dose of VIR-7831 significantly reduced the rate of progression to >24 hours of hospitalisation for acute management of any illness or death from any cause when compared with placebo *(*p=0.002*)*. The adjusted relative risk ratio of 0.15 (97.24% CI:

0.04, 0.56) indicates an 85% reduction (Table 7).

Table 7 – Summary of proportion of participants with progression COVID-19 through day 29 as evidence by hospitalisation for >24 hours or death (ITT [IA])

	Placebo (N = 292)	VIR-7831 500 mg (N = 291)
Number of Participants	292	291
Progression Status, n (%)		
Hospitalised >24 hours or Death, due to any cause	21 (7%)	3 (1%)
Hospitalised >24 hours for acute management of any illness	21 (7%)	3 (1%)
Death due to any cause	1 (<1%)	0
Alive and not hospitalised	270 (92%)	284 (98%)
Missing[a]	1 (<1%)	4 (1%)
VIR-7831 500 mg vs. Placebo [b]		
Adjusted Relative Risk Ratio	0.15	
97.24% Confidence Interval	(0.04, 0.56)	
p-value	0.002	

Interim Analysis 1 DCO: 04 March 2021.

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 3 participants randomised to receive VIR-7831 and 1 participant randomised to received placebo withdrew consent prior to dosing and 1 participant treated with VIR-7831 withdrew consent by Day 8.

b. Relative risk ratio was calculated with respect to participants hospitalised >24 hours or dead.

Note: Relative risk ratio is presented using a Poisson regression model with a robust sandwich estimator, adjusted for treatment (VIR-7831 vs. placebo), duration of symptoms (≤3 days vs. ≥4 days), age (≤70 vs. >70 years old) and gender (female vs. male) as covariates. Available data were used in the analysis as collected, regardless of the occurrence of intercurrent events. Missing data were imputed under a missing at random (MAR) assumption, using multiple imputation (MI).

Subgroup analysis

Summaries for the primary endpoint were performed for baseline subgroups stratified by duration of symptoms (≤3 days vs. ≥ 4 days) (Table 8). Subgroup summary results were generally consistent with those reported in the overall population and show no difference in effect size according to the duration of symptoms prior to study enrolment.

Of note, as 24 hours were allowed between randomisation and dosing, participants may have been dosed up to 6 days after the onset of symptoms.

Table 8 – Summary of proportion of participants who have progression of COVID-19 (hospitalisation >24 hours or death) at day 29 by duration of symptoms (ITT [IA])

	Placebo (N=292)		VIR-7831 500 mg (N=291)	
	Days from onset of symptoms		Days from onset of symptoms	
Day 29	≤3 days	≥4 days	≤3 days	≥4 days
Number of Participants	171	121	167	124
Progression Status, n (%)				
Hospitalised >24 hours or Death, due to any cause	12 (7%)	9 (7%)	2 (1%)	1 (<1%)
Hospitalised >24 hours for acute management of any illness	12 (7%)	9 (7%)	2 (1%)	1 (<1%)
Death due to any cause	0	1 (<1%)	0	0
Alive and not hospitalised	159 (93%)	111 (92%)	164 (98%)	120 (97%)
Missing[a]	0	1 (<1%)	1 (<1%)	3 (2%)

Interim Analysis 1 DCO: 04 March 2021.

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 3 participants randomised to receive VIR-7831 and 1 participant randomised to receive placebo withdrew consent prior to dosing and 1 participant treated with VIR-7831 with ≥4 days duration of symptoms withdrew consent by Day 8.

Note: Participants are counted in each subcategory of progression experienced up to the time point in question and may be included in more than one category.

Secondary endpoint analyses (emergency room visit, hospitalisation or death)

Treatment with VIR-7831 resulted in a numerical reduction in need for hospital Emergency Room (ER) visits for management of illness or hospitalisation for acute management of illness (any duration) or death (any cause) compared to placebo (Table 9). Most patients in the placebo arm were hospitalised due to COVID-19 progression (Table 10). The exceptions were one patient with pulmonary embolism and three with pneumonia unspecified for whom no aetiology aside from underlying COVID-19 was found so they may also have represented pneumonia due to COVID-19. In the VIR-7831 group two patients were hospitalised due to progression of symptoms of underlying COVID-19.

Table 9 – Summary and proportion of participants who have progression of COVID-19 through day 29 (visit to hospital emergency room, hospitalisation or death) (ITT [IA])

	Placebo (N=292)	VIR-7831 500 mg (N=291)
Number of Participants	292	291
Progression Status, n (%)		
Hospitalised, ER visit or Death, due to any cause	28 (10%)	6 (2%)
Hospitalised for acute management of any illness, any duration	21 (7%)	4 (1%) [a]
ER visit due to any cause	8 (3%)	2 (<1%)
Death due to any cause	1 (<1%)	0
Alive and not hospitalised and no ER visit	263 (90%)	281 (97%)
Missing[b]	1 (<1%)	4 (<1%)

Interim Analysis 1 DCO: 04 March 2021.

a. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant (11630) was hospitalised for <24 hours for hyperglycaemia
b. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 3 participants randomised to receive VIR-7831 and 1 participant randomised to received placebo withdrew consent prior to dosing and 1 participant treated with VIR-7831 withdrew consent by Day 8.

Table 10 – Summary of reasons for hospitalisation of any duration (ITT [IA])

	Placebo (N=292)	VIR-7831 500 mg (N=291)
Number of Participants Hospitalised	21	4
Reason for Hospitalisation (SAE preferred term)		
COVID-19	0	1 (<1%)
COVID-19 pneumonia	13 (4%)	1 (<1%)
Small intestinal obstruction	0	1 (<1%)
Diabetes mellitus	0	1 (<1%)
Acute respiratory failure	1 (<1%)	0
Dehydration	1 (<1%)	0
Dyspnoea[a]	1 (<1%)	0
Hypovolaemia[a]	1 (<1%)	0
Pneumonia	3 (1%)	0
Pulmonary embolism	1 (<1%)	0
Respiratory distress	1 (<1%)	0

Interim Analysis 1 DCO: 04 March 2021.

a Participant 13102 reported hypovolaemia and dyspnoea

Subgroup results stratified by duration of symptoms were generally consistent with those reported in the overall population (Table 11).

Table 11 – Summary of proportion of participants who have progression of COVID-19 through day 29 (hospitalisation or emergency room visit or death) by duration of symptoms (ITT [IA])

	Placebo (N=292)		VIR-7831 500 mg (N=291)	
	Days from onset of symptoms		Days from onset of symptoms	
Day 29	≤3 days	≥4 days	≤3 days	≥4 days
Number of Participants	171	121	167	124
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	17 (10%)	11 (9%)	4 (2%)	2 (2%)
Hospitalised for acute management of any illness, any duration	12 (7%)	9 (7%)	3[a] (2%)	1[a] (<1%)
ER visit due to any cause	6 (4%)	2 (2%)	1 (<1%)	1 (<1%)
Death due to any cause	0	1 (<1%)	0	0
Alive and not hospitalised and no ER visit	154 (90%)	109 (90%)	162 (97%)	119 (96%)
Missing[b]	0	1 (<1%)	1 (<1%)	3 (2%)

Interim Analysis 1 DCO: 04 March 2021.

a. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant (11630) was hospitalised for <24 hours for hyperglycaemia

b. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 3 participants randomised to receive VIR-7831 and 1 participant randomised to received placebo withdrew consent prior to dosing and 1 participant treated with VIR-7831 withdrew consent by Day 8.

Note: Participants are counted in each subcategory of progression experienced up to the time point in question and so may be included in more than one category.

Secondary endpoint analyses (severe and/or critical respiratory COVID-19)

Treatment with VIR-7831 resulted in numerical reduction in the risk of severe and/or critical respiratory COVID-19 (Table 12). Specifically, no participants treated with VIR-7831 required high flow oxygen, oxygen via a non-rebreather mask or mechanical ventilation through Day 29. Two patients in the placebo arm required mechanical ventilation. No patients in the study required ECMO.

Subgroup summary results stratified by duration of symptoms (≤3 days vs. ≥4 days) were generally consistent with those reported in the overall population (Table 13).

Table 12 – Summary of proportion of participants who progress to develop severe and/or critical respiratory COVID-19 by visit at day 8, day 15, day 22, or day 29 (ITT [IA])

	Day 8		Day 15		Day 22		Day 29	
	Placebo (N=292)	VIR-7831 500 mg (N=291)	Placebo (N=292)	VIR-7831 500 mg (N=291)	Placebo (N=292)	VIR-7831 500 mg (N=291)	Placebo (N=292)	VIR-7831 500 mg (N=291)
Number of Participants	292	291	292	291	292	291	292	291
Progression Status, n (%)								
No Severe/Critical Progression [a]	278 (95%)	286 (98%)	272 (93%)	286 (98%)	272 (93%)	285 (98%)	272 (93%)	285 (98%)
Severe/Critical progression [b]	13 (4%)	1 (<1%)	19 (7%)	1 (<1%)	19 (7%)	2 (<1%)	19 (7%)	2 (<1%)
Category 2: Low flow nasal cannulae/face mask (severe)	7 (2%)	1 (<1%)	11 (4%)	1 (<1%)	11 (4%)	2 (<1%)	11 (4%)	2 (<1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	6 (2%)	0	6 (2%)	0	5 (2%)	0	5 (2%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	0	0	2 (<1%)	0	2 (<1%)	0	2 (<1%)	0
Death	0	0	0	0	1 (<1%)	0	1 (<1%)	0
Missing	1 (<1%)	4 (<1%)	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)

Interim Analysis 1 DCO: 04 March 2021

a. All participants status at admission is Category 1: Room air.
b. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.

Note: Participants with progression are counted in the worst-case progression that they have reported up to the relevant time point.

Table 13 – Summary of proportion of subjects who progress to develop severe and/or critical respiratory COVID-19 at ay 29 duration of symptoms (ITT [IA])

	Day 29			
	Placebo (N=292)		VIR-7831 500 mg (N=291)	
	Days from onset of symptoms		Days from onset of symptoms	
Day 29	≤3 days	≥4 days	≤3 days	≥4 days
Number of Participants	171	121	167	124
Progression Status, n (%)				
No Severe/Critical Progression[a]	160 (94%)	112 (93%)	165 (99%)	120 (97%)
Severe/Critical progression[b]	11 (6%)	8 (7%)	1 (<1%)	1 (<1%)
Category 2: Low flow nasal cannulae/face mask (severe)	8 (5%)	3 (2%)	1 (<1%)	1 (<1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	1 (<1%)	4 (3%)	0	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	2 (<1%)	0	0	0
Death	0	1 (<1%)	0	0
Missing[c]	0	1 (<1%)	1 (<1%)	3 (2%)

Interim Analysis 1 DCO: 04 March 2021

a. All participants status at admission is Category 1: Room air.
b. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
c. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 3 participants randomised to receive VIR-7831 and 1 participant randomised to received placebo withdrew consent prior to dosing and 1 participant treated with VIR-7831 withdrew consent by Day 8.

Note: Participants with progression are counted in the worst-case progression that they have reported up to the relevant time point.

Exploratory secondary endpoints analyses (Length of hospital stay, Duration of ventilation, Length of ICU stay)

Amongst those who required hospitalisation, treatment with VIR-7831 resulted in a numerical reduction in the duration of hospitalisation when compared to placebo (Table 14).

No participants in the VIR-7831 arm required mechanical ventilator support or ECMO while hospitalised vs. 2 (<1%) participants in the placebo arm (Table 15).

No participants in the VIR-7831 arm required an ICU stay vs. 5 (2%) participants in the placebo arm (Table 16).

Table 14 – Summary of duration in hospital from randomisation through day 29 days (ITT [IA])

	Placebo (N=292)	VIR-7831 500 mg (N=291)
Alive and never entered hospital[a]	270 (92%)	283 (97%)
Entered hospital (any duration), n (%)	21 (7%)	4 (1%)
1 stay	21 (7%)	4 (1%)
Hospital stay, n (%)[b]		
0 days	271 (93%)	287 (99%)
>0 to≤24 hours	0	1 (<1%)
1 to ≤8 days	16 (5%)	1 (<1%)
9 to ≤15 days	0	1 (<1%)
16 to ≤22 days	3 (<1%)	1 (<1%)
23 to ≤29 days	2 (<1%)	0
Incomplete follow-up due to study withdrawal[c]	3 (1%)	4 (1%)
Incomplete follow-up due to death	1 (<1%)	0

Interim Analysis 1 DCO: 04 March 2021

a. Alive and no in-patient hospital stays based on complete follow-up data
b. Participants who died prior to date of randomisation + 28 days were considered to be in hospital from date of death until date of randomisation+ 28 days.
c. Includes the 5 missing participants for the primary endpoint (randomised but not treated [VIR-7831: 3; placebo: 1]; 1 participant treated with VIR-7831 withdrew consent by Day 8) and an additional 2 participants in the placebo arm who were hospitalised at Day 15 and Day 16 and subsequently withdrew consent.

Table 15 – Summary of duration on ventilation from randomisation through day 29 days

	Placebo (N=292)	VIR-7831 500 mg (N=291)
Alive and never on ventilator[a]	286 (98%)	287 (99%)
On ventilator, n (%)	2 (<1%)	0
Ventilator use, n (%)[b]		
0 days	289 (99%)	291 (100%)
1 to ≤8 days	0	0
9 to ≤15 days	2 (<1%)	0
16 to ≤22 days	1 (<1%)	0
23 to ≤29 days	0	0
Incomplete follow-up due to study withdrawal[b]	3 (1%)	4 (1%)
Incomplete follow-up due to death	1 (<1%)	0

Interim Analysis 1 DCO: 04 March 2021

a. Alive and never on a ventilator based on complete follow-up data
b. Includes the 5 missing participants for the primary endpoint (randomised but not treated [VIR-7831: 3; placebo: 1]; 1 participant treated with VIR-7831 withdrew consent by Day 8) and an additional 2 participants in the placebo arm who were hospitalised at Day 15 and Day 16 and subsequently withdrew consent.

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Table 16 – Summary of duration in intensive care unit from randomisation through day 29

	Placebo (N=292)	VIR-7831 500 mg (N=291)
Alive and never entered ICU[a]	284 (97%)	287 (99%)
Entered ICU, n (%)	5 (2%)	0
ICU stay, n (%)[b]		
0 days	287 (98%)	291 (100%)
1 to ≤8 days	1 (<1%)	0
9 to ≤15 days	2 (<1%)	0
16 to ≤22 days	1 (<1%)	0
23 to ≤29 days	1 (<1%)	0
Incomplete follow-up due to study withdrawal[b]	3 (1%)	4 (1%) [b]
Incomplete follow-up due to death	1 (<1%)	0

Interim Analysis 1 DCO: 04 March 2021

a. Alive and no ICU stays based on complete follow-up data
b. Includes the 5 missing participants for the primary endpoint (randomised but not treated [VIR-7831: 3; placebo: 1]; 1 participant treated with VIR-7831 withdrew consent by Day 8) and an additional 2 participants in the placebo arm who were hospitalised at Day 15 and Day 16 and subsequently withdrew consent.

Secondary endpoint analyses (All-Cause Mortality up to Day 29)

No deaths were reported in the VIR-7831 treatment arm, whereas 1 death was reported in the placebo arm (Table 17).

Table 17 – Summary all-cause mortality up to day 29 (ITT [IA])

Parameter	Placebo (N=292)	VIR-7831 500 mg (N=291)
Number of Participants		
Deceased	1 (<1%)	0
Alive at Day 29[a]	288 (99%)	187 (99%)
Censored at Study Withdrawal[b]	3 (1%)	4 (1%)

Interim Analysis 1 DCO: 04 March 2021.

a. Participants alive at end of follow-up were censored at Day 29, respectively.
b. Censored at Study withdrawal includes the 5 missing participants for the primary endpoint (randomised but not treated [VIR-7831: 3; placebo: 1]; 1 participant treated with VIR-7831 withdrew consent by Day 8) and an additional 2 participants in the placebo arm who were hospitalised at Day 15 and Day 16 and subsequently withdrew consent.

Secondary endpoint analysis (Change from baseline in viral load in nasal secretions by qRT-PCR up to day 8

The virology (IA) population (N=324) is a subset of the ITT (IA) analysis set, which includes participants with a central laboratory confirmed quantifiable nasopharyngeal swab at Day 1. This

subset is currently limited by the availability of baseline, Day 5 and Day 8 viral load data due to analysis turnaround times.

The preliminary data indicate that baseline viral load was similar across treatment arms. The mean decline in viral load from baseline at Day 8 was numerically greater in VIR-7831-treated patients than for patients treated with placebo (Table 18).

Table 18 – Preliminary summary of change from baseline in viral load in nasal secretions by qRT-PCR through day 8 (virology [IA])

	Placebo N=170	VIR-7831 (500 mg IV) N=154
Baseline (log 10 copies/mL)		
n	170	154
Mean (standard deviation)	6.833 (1.7049)	6.682 (1.6555)
Median (Min, Max)	7.126 (3.367, 9.839)	6.853 (3.412, 9.985)
Day 5 (log 10 copies/mL)		
n	105	109
Mean (standard deviation)	5.145 (2.1394)	4.568 (2.2845)
Median (Min, Max)	5.160 (0.000, 9.423)	5.058 (0.000, 8.830)
Day 5 change from baseline (log 10 copies/mL)		
n	105	109
Mean (standard deviation)	-1.803 (1.5565)	-2.210 (1.7157)
Median (Min, Max)	-1.819 (-5.941, 2.917)	-1.989 (-6.917, 3.306)
Day 8 (log 10 copies/mL)		
n	106	98
Mean (standard deviation)	4.243 (1.8622)	3.853 (1.9736)
Median (Min, Max)	4.400 (0.000, 7.796)	4.336 (0.000, 8.231)
Day 8 change from baseline (log 10 copies/mL)		
n	106	98
Mean (standard deviation)	-2.878 (1.6411)	-2.996 (1.6527)
Median (Min, Max)	-2.883 (-6.685, 1.181)	-3.277 (-6.917, 0.925)

Interim Analysis 1 DCO: 04 March 2021

Note: Detectable values less than the lower limit of quantification (LLQ=2228 copies/mL) have been imputed to 0.5xLLQ prior to taking the log 10 value. 'Not detectable' results have been imputed to 1 prior to taking the log 10 value

Subgroup results stratified by baseline viral load showed some inconsistency (Table 19). As such, the numerical decrease in viral load at day 8 was larger for the placebo group in subjects with Baseline SARS-CoV-2 Viral Load (copies/mL) of $\log10^5$ to $\log10^6$ and viral load > $\log10^7$, whereas the treatment difference was in favour of VIR-7831 in subjects with viral load ≤ $\log10^5$ and viral load of $\log10^6$ to $\log10^7$.

Table 19 – Preliminary summary of change from baseline in nasal SARS-CoV-2 viral load through day 8 by baseline viral load (virology [IA])

SARS-CoV-2 Viral Load (log 10 copies/mL)		Placebo (N=170)	VIR-7831 500 mg (N=154)
Baseline SARS-CoV-2 Viral Load (copies/mL):≤log10^6 copies/mL			
Baseline	n	33	28
	Mean (SD)	4.256 (0.4679)	4.251 (0.4768)
	Median (Min, Max)	4.244 (3.367, 4.945)	4.284 (3.412, 4.949)
Change from Baseline at:			
Day 5	n	17	18
	Mean (SD)	-1.806 (2.4117)	-2.151 (2.4133)
	Median (Min, Max)	-1.376 (-4.945, 2.917)	-2.272 (-4.794, 3.306)
Day 8	n	13	14
	Mean (SD)	-1.802 (2.1421)	-2.851 (2.0156)
	Median (Min, Max)	-1.338 (-4.741, 1.181)	-3.655 (-4.949, 0.426)
Baseline SARS-CoV-2 Viral Load (copies/mL): >log10^6 copies/mL- ≤log 10^8			
Baseline	n	23	29
	Mean (SD)	5.488 (0.3296)	5.476 (0.3053)
	Median (Min, Max)	5.428 (5.044, 5.947)	5.463 (5.001, 5.946)
Change from Baseline at:			
Day 5	n	16	23
	Mean (SD)	-1.549 (1.9044)	-2.216 (1.8331)
	Median (Min, Max)	-1.332 (-5.941, 1.004)	-1.641 (-5.498, 1.120)
Day 8	n	16	19
	Mean (SD)	-2.538 (2.1717)	-2.166 (1.9505)
	Median (Min, Max)	-1.763 (-5.941, -0.070)	-1.557 (-5.915, 0.925)
Baseline SARS-CoV-2 Viral Load (copies/mL): >log10^8 copies/mL- ≤log 10^9			
Baseline	n	24	26
	Mean (SD)	6.501 (0.2753)	6.549 (0.2930)
	Median (Min, Max)	6.483 (6.120, 6.998)	6.581 (6.088, 6.984)
Change from Baseline at:			
Day 5	n	14	14
	Mean (SD)	-1.208 (0.8326)	-1.771 (2.3327)
	Median (Min, Max)	-1.302 (-2.733, 0.420)	-1.395 (-6.917, 0.995)
Day 8	n	15	16
	Mean (SD)	-2.250 (1.4866)	-3.159 (2.0390)
	Median (Min, Max)	-2.182 (-6.685, -0.101)	-3.036 (-6.917, 0.209)
Baseline SARS-CoV-2 Viral Load (copies/mL): >log10^9 copies/mL			
Baseline	n	90	71
	Mean (SD)	8.210 (0.7185)	8.182 (0.7606)
	Median (Min, Max)	8.320 (7.018, 9.839)	8.139 (7.020, 9.985)
Change from Baseline at:			
Day 5	n	58	54
	Mean (SD)	-2.015 (1.2349)	-2.340 (1.1540)
	Median (Min, Max)	-2.176 (-4.305, 0.880)	-2.364 (-4.880, 1.741)
Day 8	n	62	49
	Mean (SD)	-3.343 (1.2136)	-3.307 (1.1435)
	Median (Min, Max)	-3.515 (-5.301, -0.169)	-3.470 (-5.093, -0.220)

Interim Analysis 1 DCO: 04 March 2021

Note: Values less than the lower limit of quantification (LLQ=2228 copies/mL) have been imputed to 0.5xLLQ prior to taking the log 10 value. 'Not detectable' results have been imputed to 1 prior to taking the log 10 value.
Participants with progression are counted in the worst-case progression that they have reported up to the relevant time point.

Subgroup summary results stratified by duration of symptoms were generally consistent with those reported in the overall population (Table 20).

Table 20 – Preliminary summary of change from baseline in viral load (log 10 copies/mL) in nasal secretions by qRT-PCR through day 8 by duration of symptoms (Virology [IA])

	Placebo N=170		VIR-7831 (500 mg IV) N=154	
	Days from onset of symptoms		Days from onset of symptoms	
	≤3 days	≥4 days	≤3 days	≥4 days
Baseline (log 10 copies/mL)				
n	96	74	93	61
Mean (standard deviation)	6.995 (1.6597)	6.624 (1.7510)	6.815 (1.6422)	6.479 (1.6685)
Median (Min, Max)	7.248 (3.419, 9.608)	7.008 (3.367, 9.839)	7.020 (3.504, 9.985)	6.596 (3.412, 9.773)
Day 5 (log 10 copies/mL)				
n	65	40	70	39
Mean (standard deviation)	5.407 (2.1813)	4.720 (2.0242)	4.460 (2.1244)	4.761 (2.5646)
Median (Min, Max)	5.710 (0.000, 9.011)	4.993 (0.000, 9.423)	4.989 (0.000, 8.386)	5.463 (0.000, 8.830)
Day 5 change from baseline (log 10 copies/mL)				
n	65	40	70	39
Mean (standard deviation)	-1.785 (1.5797)	-1.830 (1.5377)	-2.443 (1.4881)	-1.791 (2.0162)
Median (Min, Max)	-1.764 (-5.941, 2.917)	-1.821 (-5.727, 0.880)	-2.199 (-6.180, 0.810)	-1.563 (-6.917, 3.306)
Day 8 (log 10 copies/mL)				
n	66	40	63	35
Mean (standard deviation)	4.214 (2.1610)	4.291 (1.2446)	3.703 (2.0795)	4.122 (1.7638)
Median (Min, Max)	4.562 (0.000, 7.796)	4.229 (0.000, 7.007)	4.215 (0.000, 8.231)	4.464 (0.000, 6.779)
Day 8 change from baseline (log 10 copies/mL)				
n	66	40	63	35
Mean (standard deviation)	-3.018 (1.6305)	-2.647 (1.6530)	-3.082 (1.4939)	-2.842 (1.9195)
Median (Min, Max)	-3.060 (-6.685, 1.181)	-2.449 (-5.276, 0.482)	-3.470 (-5.915, 0.925)	-2.931 (-6.917, 0.426)

Interim Analysis 1 DCO: 04 March 2021

Note: Detectable values less that the lower limit of quantification (LLQ=2228 copies/mL) have been imputed to 0.5xLLQ prior to taking the log 10 value. 'Not detectable' results have been imputed to 1 prior to taking the log 10 value

Post-hoc subgroup analysis

Post-hoc analyses stratified by age (≤70 years / >70 years) showed that the proportion of participants that was hospitalised >24 hours or died (primary endpoint) was higher in the older participants than younger participants (Table 21). The primary endpoint occurred in 7% vs 0.4% of participants ≤70 years and in 9% vs 6% in participants >70 years for placebo vs VIR-7831.

Table 21 – Summary of primary and key secondary efficacy endpoints by randomised age group (≤70, >70 years) (day 29) (ITT[IA])

	Placebo (N=292)		Sotrovimab (500 mg IV) (N=291)	
	Age		Age	
Day 29	≤70 years	>70 years	≤70 years	>70 years
Number of Participants	260	32	258	33
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death)				
Progression Status, n (%)				
..Hospitalised >24 hours or Death, due to any cause	18 (7%)	3 (9%)	1 (<1%)	2 (6%)
Hospitalised >24 hours for acute management of any illness	18 (7%)	3 (9%)	1 (<1%)	2 (6%)
Death due to any cause	1 (<1%)	0	0	0
..Alive and not hospitalised >24 hours	241 (93%)	29 (91%)	253 (98%)	31 (94%)
..Missing[a]	1 (<1%)	0	4 (2%)	0
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	24 (9%)	4 (13%)	4 (2%)	2 (6%)
Hospitalised for acute management of any illness, any duration	18 (7%)	3 (9%)	2 (<1%)[b]	2 (6%)[b]
ER visit due to any cause	7 (3%)	1 (3%)	2 (<1%)	0
Death due to any cause	1 (<1%)	0	0	0
..Alive and not hospitalised and no ER visit	235 (90%)	28 (88%)	250 (97%)	31 (94%)
..Missing[a]	1 (<1%)	0	4 (2%)	0
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19				
Progression Status, n (%)				
No Severe/Critical Progression[c]	243 (93%)	29 (91%)	254 (98%)	31 (94%)
Severe/Critical Progression[d]	16 (6%)	3 (9%)	0	2 (6%)
Category 2: Low flow nasal cannulae/face mask (severe)	9 (3%)	2 (6%)	0	2 (6%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	5 (2%)	0	0	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	1 (<1%)	1 (3%)	0	0
Death	1 (<1%)	0	0	0
..Missing[e]	1 (<1%)	0	4 (2%)	0

Interim Analysis 1 DCO: 04 March 2021.

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant (11630 ≤70 years) was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).

Note: Participants are counted in each subcategory of progression experienced up to the time point in question and may be included in more than one category.

Post hoc subgroup analysis by BMI (≤30 kg/m^2 / >30kg/m^2) showed that the proportion of participants that was hospitalised >24 hours or died (primary endpoint) was higher in the participants with a BMI ≤30 kg/m^2 (Table 22). The difference between placebo and VIR-7831 was consistent across BMI groups.

Table 22 – Summary of primary and key secondary efficacy endpoints by obesity risk factor (BMI≤30 kg/m^2, >30 kg/m^2) (day 29) (ITT [IA])

	Placebo (N=292)		Sotrovimab (500 mg IV) (N=291)	
	BMI		BMI	
Day 29	≤30 kg/m^2	>30 kg/m^2	≤30 kg/m^2	>30 kg/m^2
Number of Participants	105	187	109	182
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death)				
Progression Status, n (%)				
..Hospitalised >24 hours or Death, due to any cause	11 (10%)	10 (5%)	1 (<1%)	2 (1%)
Hospitalised >24 hours for acute management of any illness	11 (10%)	10 (5%)	1 (<1%)	2 (1%)
Death due to any cause	0	1 (<1%)	0	0
..Alive and not hospitalised >24 hours	93 (89%)	177 (95%)	108 (>99%)	176 (97%)
..Missing[a]	1 (<1%)	0	0	4 (2%)
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	12 (11%)	16 (9%)	3 (3%)	3 (2%)
Hospitalised for acute management of any illness, any duration	11 (10%)	10 (5%)	2 (2%)[b]	2 (1%)[b]
ER visit due to any cause	2 (2%)	6 (3%)	1 (<1%)	1 (<1%)
Death due to any cause	0	1 (<1%)	0	0
..Alive and not hospitalised and no ER visit	92 (88%)	171 (91%)	106 (97%)	175 (96%)
..Missing[a]	1 (<1%)	0	0	4 (2%)
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19				
Progression Status, n (%)				
No Severe/Critical Progression[c]	95 (90%)	177 (95%)	108 (>99%)	177 (97%)
Severe/Critical Progression[d]	9 (9%)	10 (5%)	1 (<1%)	1 (<1%)
Category 2: Low flow nasal cannulae/face mask (severe)	7 (7%)	4 (2%)	1 (<1%)	1 (<1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	1 (<1%)	4 (2%)	0	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	1 (<1%)	1 (<1%)	0	0
Death	0	1 (<1%)	0	0
Missing[e]	1 (<1%)	0	0	4 (2%)

Interim Analysis 1 DCO: 04 March 2021.

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant (11630 ≤30 kg/m^2) was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).

Note: Participants are counted in each subcategory of progression experienced up to the time point in question and may be included in more than one category.

Post hoc subgroup analysis by diabetes diagnosis (yes/no) showed that the proportion of participants that was hospitalised >24 hours or died (primary endpoint) was higher in participants with diabetes (Table 23). The difference between placebo and VIR-7831 was consistent across the two subgroups.

Table 23 – Summary of primary and key secondary efficacy endpoints by presence of diabetes requiring medication risk factor (day 29) (ITT [IA])

	Placebo (N=292)		Sotrovimab (500 mg IV) (N=291)	
	Presence of Diabetes Requiring Medication		Presence of Diabetes Requiring Medication	
Day 29	Yes	No	Yes	No
Number of Participants	66	226	66	225
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death)				
Progression Status, n (%)				
..Hospitalised >24 hours or Death, due to any cause	9 (14%)	12 (5%)	3 (5%)	0
Hospitalised >24 hours for acute management of any illness	9 (14%)	12 (5%)	3 (5%)	0
Death due to any cause	0	1 (<1%)	0	0
..Alive and not hospitalised >24 hours	57 (86%)	213 (94%)	63 (95%)	221 (98%)
..Missing[a]	0	1 (<1%)	0	4 (2%)
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	11 (17%)	17 (8%)	4 (6%)	2 (<1%)
Hospitalised for acute management of any illness, any duration	9 (14%)	12 (5%)	4 (6%)[b]	0
ER visit due to any cause	2 (3%)	6 (3%)	0	2 (<1%)
Death due to any cause	0	1 (<1%)	0	0
..Alive and not hospitalised and no ER visit	55 (83%)	208 (92%)	62 (94%)	219 (97%)
..Missing[a]	0	1 (<1%)	0	4 (2%)
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19				
Progression Status, n (%)				
No Severe/Critical Progression[c]	59 (89%)	213 (94%)	64 (97%)	221 (98%)
Severe/Critical Progression[d]	7 (11%)	12 (5%)	2 (3%)	0
Category 2: Low flow nasal cannulae/face mask (severe)	4 (6%)	7 (3%)	2 (3%)	0
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	3 (5%)	2 (<1%)	0	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	0	2 (<1%)	0	0
Death	0	1 (<1%)	0	0
Missing[e]	0	1 (<1%)	0	4 (2%)

Interim Analysis 1 DCO: 04 March 2021.

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant (11630: diabetes requiring medication) was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).

Note: Participants are counted in each subcategory of progression experienced up to the time point in question and may be included in more than one category.

Post-hoc subgroup analysis by asthma diagnosis (yes/no) showed no marked differences between participants with and without asthma (Table 24), and the difference between placebo and VIR-7831 was consistent across the two subgroups.

Table 24 – Summary of primary and key secondary efficacy endpoints by presence of moderate to severe asthma risk factor (day 29) (ITT [IA])

	Placebo (N=292)		Sotrovimab (500 mg IV) (N=291)	
	Moderate to Severe Asthma		Moderate to Severe Asthma	
Day 29	Yes	No	Yes	No
Number of Participants	46	246	46	245
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death)				
Progression Status, n (%)				
Hospitalised >24 hours or Death, due to any cause	3 (7%)	18 (7%)	0	3 (1%)
Hospitalised >24 hours for acute management of any illness	3 (7%)	18 (7%)	0	3 (1%)
Death due to any cause	1 (2%)	0	0	0
Alive and not hospitalised >24 hours	42 (91%)	228 (93%)	46 (100%)	238 (97%)
Missing[a]	1 (2%)	0	0	4 (2%)
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	3 (7%)	25 (10%)	0	6 (2%)
Hospitalised for acute management of any illness, any duration	3 (7%)	18 (7%)	0	4 (2%)[b]
ER visit due to any cause	0	8 (3%)	0	2 (<1%)
Death due to any cause	1 (2%)	0	0	0
Alive and not hospitalised and no ER visit	42 (91%)	221 (90%)	46 (100%)	235 (96%)
Missing[a]	1 (2%)	0	0	4 (2%)
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19				
Progression Status, n (%)				
No Severe/Critical Progression[c]	42 (91%)	230 (93%)	46 (100%)	239 (98%)
Severe/Critical Progression[d]	3 (7%)	16 (7%)	0	2 (<1%)
Category 2: Low flow nasal cannulae/face mask (severe)	1 (2%)	10 (4%)	0	2 (<1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	1 (2%)	4 (2%)	0	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	0	2 (<1%)	0	0
Death	1 (2%)	0	0	0
Missing[e]	1 (2%)	0	0	4 (2%)

Interim Analysis 1 DCO: 04 March 2021.

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant (11630: not asthmatic) was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).

Note: Participants are counted in each subcategory of progression experienced up to the time point in question and may be included in more than one category.

Emergence of Viral Resistance Mutants to mAb by SARS-CoV-2

Sequence analysis of the SARS-CoV-2 spike gene to monitor for potential resistance mutations is currently available on nasal samples from 126 participants in the COMET-ICE study. Additional data is being collected. These 126 samples comprise 104 (18% of participants) baseline samples (VIR-7831: 48; placebo: 56) and 48 (8%) post-baseline samples (VIR-7831: 28; placebo: 20; representing 26 and 18 participants, respectively).

In the currently available baseline sequencing dataset:

- None of the sequenced participants carried the SARS-CoV-2 UK (B.1.1.7), South Africa (B.1.351) or Brazil (P.1) variants. Pseudotyped virus data indicate that VIR-7831 retains activity against these variants *in vitro*.
- Four participants had baseline sequences consistent with the presence of the CAL.20C (the Californian, red.) variant (VIR-7831: 1; placebo: 3). The VIR-7831 participant was not hospitalised and did not have ER visits. Pseudotyped virus data indicate that VIR-7831 retains activity against these variants *in vitro*.

- VIR-7831 epitope amino acid variants present at baseline were detected in 2 of 104 participants with available baseline sequences (1.9%) at an allelic fraction (AF) >15%. L335F (AF=15.2%) and C361F (15.2%) were detected in one placebo arm participant while S359G (AF=27.4%) was detected in a second placebo arm participant. No epitope variants were detected at baseline in sequences from 48 participants in the VIR-7831 treatment arm at an AF>15%.
- In the currently available post-baseline sequencing dataset, the VIR-7831 epitope variant E340K (AF=99.8%) was detected in 1 participant who received VIR-7831, but the baseline sequence is not currently available. This participant did not have an ER visit and was not hospitalised. Of the variants detected at baseline and post-baseline, L335F and E340K have been assessed phenotypically using a pseudotyped virus system; C361F and S359G have not yet been assessed. VIR-7831 retains susceptibility against L335F (0.8-fold change in EC50) while E340K confers reduced susceptibility to VIR-7831 (>297-fold change in EC50) *in vitro*. The clinical impact of these variants is not yet known.

2.2.3. Conclusions on Efficacy

The primary objective of COMET-ICE was to evaluate the efficacy of sotrovimab (VIR-7831/GSK4182136) versus placebo in preventing the progression of COVID-19 in non-hospitalised subjects with oxygen saturation ≥94% on room air.

The COMET-ICE study was the subject of three rapid CHMP scientific advice procedures. In the last of these procedures, the company proposed a change in the primary endpoint, which the CHMP was not in agreement with. The initial primary endpoint was based on progression to requirement for some level of oxygen supplementation or death. This was defined as development of oxygen saturation <94% on room air on two occasions at least 8 hours apart or hospitalisation requiring some form of oxygen supplementation or death within the 28-day follow-up period. This primary endpoint was deemed appropriate and was agreed. The revised primary endpoint that required only hospitalisation >24 hours or death was considered suboptimal. This was not only because of different thresholds for hospital admission and discharge in different healthcare systems but also because some patients are hospitalised simply because they cannot be cared for at home for some reason or as a precaution because of other conditions.

Furthermore, the randomisation was not stratified by study centre (only by region). If the hospitalisation differs between study centres due to e.g. differences in health care systems (which most likely is the case) and if the randomisation is not well balanced by study centre, the endpoint will be biased.

Due to these concerns regarding the lack of sensitivity of the final primary endpoint to detect a true effect of the intervention on the course of COVID-19, it is of importance to consider the documented effects on the secondary endpoints, several of which capture real changes in clinical condition rather than placement of the patient.

With no prior human experience with this engineered IgG1 monoclonal antibody, the use of a Lead-in phase and Expansion phase was considered to be appropriate by CHMP. From the sample size calculation and information provided in the protocol, the Lead-in phase subjects were included in the primary analysis. It would have been preferred that the Lead-in phase patients were excluded from the primary analysis of efficacy. Although they were subject to the same selection criteria, they spent the first 7 days in hospital due to the additional monitoring procedures. Therefore, they could not be

adequately assessed for the primary endpoint. Nevertheless, with only 10 per treatment group, it is unlikely they would have an influence in the findings of IA1 that was based on 583 patients.

The plans for the interim analyses were found broadly acceptable. It was considered of importance that analyses for futility were planned due to lack of any data that could predict efficacy. The applicant did attempt to support the selected dose by projected exposures based on data with other monoclonal antibodies given IV and, later, using the PK data from COMET-ICE. Nevertheless, the dose rationale is weak. Notwithstanding the lack of a strong dose rationale, the efficacy shown in COMET-ICE supersedes such issues.

Based on the ITT population of 583 patients, there were very few dropouts in this single dose study. The population included 22% aged 65 years and over and 11% aged 70 years and over. The majority was overweight or obese. One of the protocol-listed risk factors was present in 58%, 2 in 30%, 3 in 9% and >3 in 2%. The study population comprised mainly overweight/obese middle-aged persons, some of whom had obesity-related diabetes and/or asthma. Very few had CHF or renal disease, and none was immunosuppressed. Moreover, evidence is lacking regarding the contribution of several of the listed risk factors to development of severe COVID. It is clear from stratified analysis that some of the risk factors (asthma and BMI>30) did not increase the risk for hospitalisation, whereas older age and diabetes were associated with a higher risk of hospitalisation in subjects with COVID-19.

The applicant proposed that sotrovimab is to be used specifically in patients with risk factors, including some that were not present in the study population. As such, the study population was not fully representative of the proposed target population:

For the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. Risk factors may include but are not limited to:

- *Advanced age*
- *Obesity*
- *Cardiovascular disease, including hypertension*
- *Chronic lung disease, including asthma*
- *Type 1 or type 2 diabetes mellitus*
- *Chronic kidney disease, including those on dialysis*
- *Chronic liver disease*
- *Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, and prolonged use of immune-weakening medications.*

However, since the conclusion of a reasonable likelihood of benefit may be extrapolated to such patients, the target population for use of sotrovimab, is considered acceptable in the context of this Article 5(3) procedure.

Subjects who have been vaccinated against COVID-19 were not allowed to be enrolled in the COMET-ICE trial. As such, no data is available in vaccinated persons.

Presence of SARS-CoV-2 was based on a local result for RT-PCR in ~88% and on antigen detection in the remainder, such that all patients had a positive result as required in the protocol for eligibility. It is regrettable that not all had RT-PCR confirmation in the central laboratory and that central laboratory confirmation was not requisite for inclusion in the primary analysis. Nevertheless, considering the

context of a pandemic, even the antigen detection test results were likely accurate in all or most cases. As ~12% had an antigen test, not all participants were sequenced at baseline and viral load were not assessed, which is a limitation. Furthermore, this information was only provided for a subset of the remainder participants in the current application. This is considered acceptable in the context of the current Article 5(3) procedure.

The planned first interim analysis (IA1) met the criteria for success. VIR-7831 resulted in a statistically significant reduction in the proportion who required >24 hours of hospitalisation for acute management of any illness or died from any cause through Day 29. The reduction was by 85% (adjusted relative risk reduction) (p=0.002). However, this 85% reduction translates into a modest absolute effect since the actual rates were 7% in the placebo group and 1% in the VIR-7831 group.

Of note that there was only one death recorded up to Day 29 (in the placebo group), which means that the primary analysis is driven by a reduction in the need for a hospital stay of at least 24 hours. Preventing a patient being hospitalised is not *per se* a discernible clinical benefit (see discussion above on change in primary endpoint). Therefore, the effect of active treatment on clinical endpoints designated as secondary is essential to support a conclusion of benefit.

The results for secondary and exploratory endpoints are in line with the overall conclusion of a modest clinical benefit based on the primary endpoint. Most importantly, VIR-7831 resulted in numerical reductions in need for supplementary oxygen and progression to severe and/or critical respiratory COVID-19. It was showed that no patient treated with VIR-7831 required high flow oxygen, oxygen via a non-rebreather mask or mechanical ventilation through Day 29 compared to 7 in total in the placebo group. Moreover, 11 placebo vs. 2 VIR-7831 patients required oxygen by mask or nasal cannulae. These results support a conclusion that VIR-7831 has some benefit on the risk of progression, even though this was not the final primary endpoint of the study.

Although 58% were enrolled when they had ≤3 days symptoms and 42% when they had 4-5 days of symptoms, the comparisons made between the two pre-planned strata must be viewed with caution due to the paucity of events. Nevertheless, it does not seem to be of relevance how long symptoms had been present at least up to 5 days, after which there are no data. In this mildly ill target population, a monoclonal antibody directed at the virus is less likely to have a significant effect on outcomes as time from onset increases. The Conditions for Use states the window within which sotrovimab was given.

The effect of VIR-7831 on viral load cannot be translated into a clinical benefit. The available data suggest that the mean decline in viral load from baseline to Day 8 was greater in the VIR-7831 group. After Day 8, there were no notable differences between VIR-7831 and placebo groups because the majority of patients started to mount an immune response against the virus that led to control of replication.

The infusion time in COMET-ICE was 60 minutes while 30 minutes are stated in the conditions for use. This is based on safety data from BLAZE-4 in which 30-minute infusion times are used and the observation that peak serum concentrations for monoclonal antibodies are independent of the infusion time. This is considered acceptable by CHMP.

In the study population that had mild disease at baseline plus one or more of the protocol-listed risk factors, there was only one death within 29 Days of treatment and two within the cut-off date, both of which occurred in patients given placebo. More extensive use of VIR-7831, and studies in populations that have moderate or severe COVID-19 at baseline, may further elucidate on its ability to prevent COVID-related deaths.

Concomitant monoclonal antibodies directed at COVID-19 were not allowed in the study but concomitant dexamethasone and remdesivir were allowed. It is although expected that dexamethasone and remdesivir were to be initiated in hospitalised patients only. In the efficacy population 5% in the VIR-7831 group and 8% in the placebo group received dexamethasone (figures were 5% and 6% in the safety population). In the efficacy population, ivermectin was reported for 2 patients (<1%) in the VIR-7831 arm and 9 (3%) in the placebo arm. In both the efficacy and safety analysis populations concomitant remdesivir was administered to no patient in the VIR-7831 arm and to 3 (<1%) patients in the placebo arm. Therefore, the effect of VIR-7831 on clinical and virological endpoints has been estimated in the absence of remdesivir. It remains to be elucidated whether combining VIR-7831 with remdesivir in the population for which remdesivir is indicated could provide a greater benefit, which is suggested as a possibility by the nonclinical data.

The applicant claimed that sotrovimab contains an LS modification that extends antibody half-life. Data from cynomolgous monkeys support this claim. In humans, the serum half-life of IgG is usually ~21 days. The human serum half-life of VIR-7831 has been projected to be >30 days but no estimate is provided. Where data is available, the mean Cmax was 219 µg/mL following a 1-hour IV infusion and the mean serum level on Day 29 was 37.2 µg/mL. The data from the Expansion phase gave a similar Day 29 estimate of 34.6 µg/mL (range: 17-54 µg/mL).

The available clinical data from COMET-ICE are insufficient to support any claims about efficacy of VIR-7831 against variants. Although COMET-ICE was conducted in UK and Brazil, where the UK and Brazil variants are highly prevalent, no UK and Brazil variants were detected in the included subjects, which is unexpected. Based on in-vitro susceptibility data and given that VIR-7831 is given once to patients with mild disease at baseline, the serum concentrations are projected to be sufficient to exert an antiviral effect against the majority of currently circulating variants until recovery from the acute illness. At present, variants with the E340K mutation are unlikely to be treatable. More data will be forthcoming, but it is not expected that the data from COMET-ICE alone can inform on the clinical effect of VIR-7831 against variants.

No clinical data in adolescents is available. However, extrapolation of data to adolescents (aged 12 years and over and weighing at least 40 kg) is considered acceptable by CHMP (please see clinical pharmacology section above).

In summary, a statistically significant effect of VIR-7831 on the pre-defined primary endpoint has been showed. This is further supported by the results obtained for the secondary endpoints (including several more relevant to patient clinical status). Overall, the available efficacy data show that VIR-7831 does have some benefit in patients who do not require oxygen supplementation.

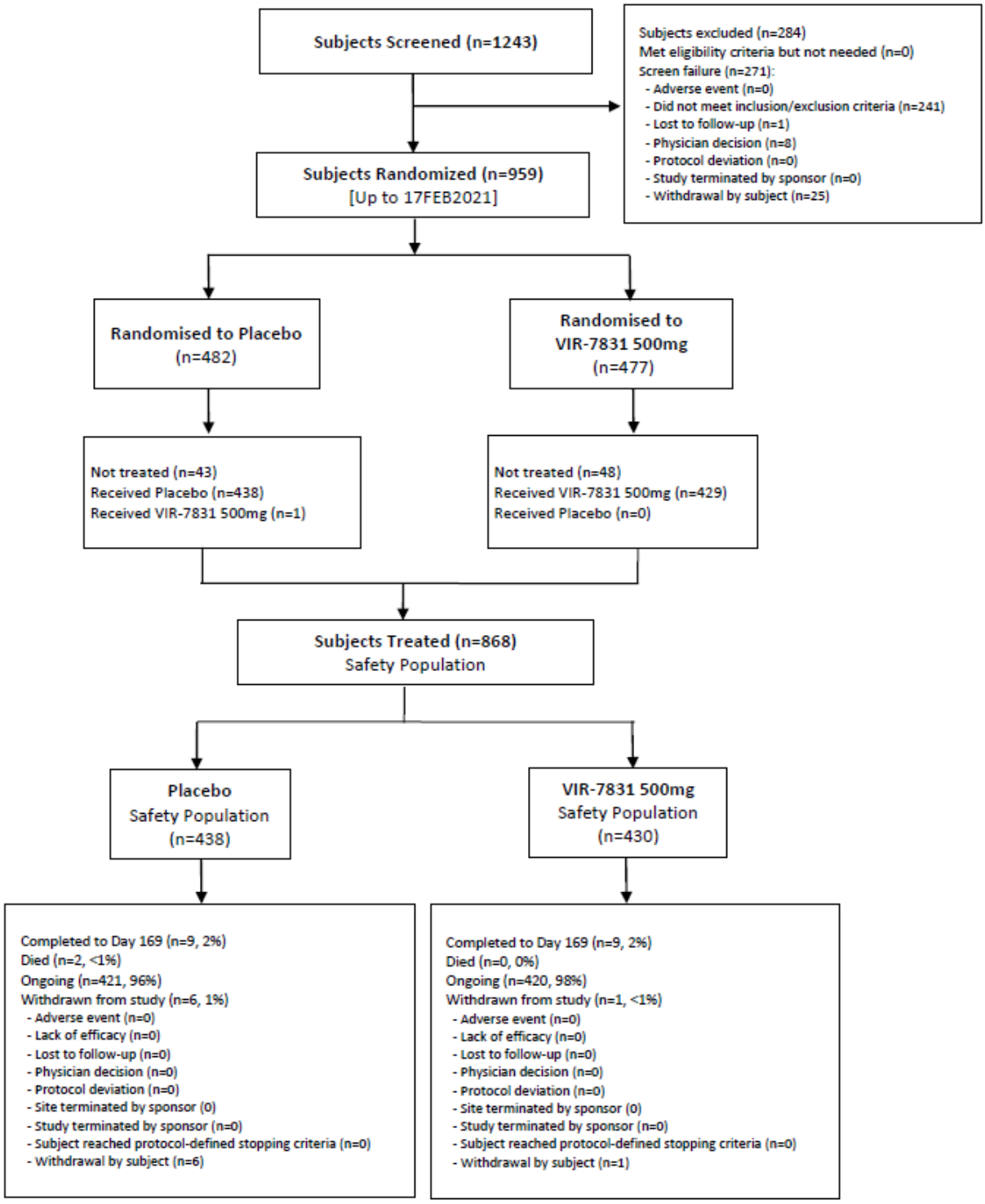
2.2.4. Data on safety

A summary of the datasets used to characterise VIR-7831 safety profile is presented below.

Table 25 - Summary of datasets used to characterise VIR-7831 safety profile at 500 mg (IV)

Dataset	Objective	Number of participants (N)
COMET-ICE (DCO: 04 March 2021)	Primary evaluation of safety data in support of Emergency Authorisation Application	N=868 (VIR-7831=430)[a]
Supportive safety information from ongoing studies		
COMET-PEAK (Part-A)- (DCO: 18 March 2021)	Additional blinded safety data in patients with mild to moderate COVID-19	N~40 (VIR-7831=5)
ACTIV-3 TICO (DCO: 23 February 2021)	Additional unblinded safety summary from hospitalised patients including exposure	N=344 (VIR-7831=168)
BLAZE-4 (DCO: 04 March 2021)	Available unblinded safety data from non-hospitalised patients including exposure (combination only, no VIR-7831 monotherapy arm)	N=202 (VIR-7831 + bamlanivimab=101)

The safety population is considerably larger than the efficacy IA1 population, comprising 868 patients (VIR-7831: 430; placebo: 438) enrolled up to 17 February 2021 and followed to the data cut-off on 04 March 2021. Patient disposition is shown below for the safety IA1 population described. The median duration of follow-up was 56 days (range 5-190) for VIR-7831 vs. 55 days (2-190) for placebo. Of the 868, 747 patients were followed through >29 days, of which 18 have been followed through 24 weeks. In addition to this, approximately 270 participants have received VIR-7831 as part of ongoing clinical trials investigating VIR-7831 as monotherapy or in combination with bamlanivimab. Available safety data from these studies were included as supporting information.



Summary of Disposition and Duration of Time on Study Post-Dose (SAF [IA])

Time on study was similar in both treatment arms. Six of the 7 withdrawals (all due to patient preference) were in the placebo arm (Table 26).

Table 26 – Summary of disposition and duration of time on study post-dose (SAF [IA])

	Placebo (N=438)	VIR-7831 500 mg (N=430)	Total (N=868)
Subject status			
Completed (Overall)[a]	9 (2%)	9 (2%)	18 (2%)
Died	2 (<1%)	0	2 (<1%)
Ongoing	421 (96%)	420 (98%)	841 (97%)
>15 days since dosing	421 (96%)	420 (98%)	841 (97%)
>29 days since dosing	364 (83%)	363 (84%)	727 (84%)
Withdrawal from study	6 (1%)	1 (<1%)	7 (<1%)
Primary reason[b] for study withdrawal			
Withdrawal by participant	6 (1%)	1 (<1%)	7 (<1%)
Duration of time on study post-dose[c]			
<5 days	1 (<1%)	0	1 (<1%)
5 to 10 days	0	1 (<1%)	1 (<1%)
11 to 14 days	0	0	0
15 to 29 days	62 (14%)	57 (13%)	119 (14%)
>29 days	375 (86%)	372 (87%)	747 (86%)
>85 days	89 (20%)	87 (20%)	176 (20%)
>141 days	11 (3%)	11 (3%)	22 (3%)
Mean (SD), days	61.2 (33.13)	62.0 (32.51)	61.6 (32.81)
Median (Min, Max),days	55.0 (2, 190)	56.0 (5, 190)	55.0 (2, 190)

Interim Analysis 1 DCO: 04 March 2021

a. Participant is considered to have completed the study if he/she completed all visits of the study through Week 24.
b. Participants may have only one primary reason for study withdrawal.
c. Duration of follow-up in the study from date of infusion through to time of study completion/withdrawal or data cut-off date if participant still ongoing in the study.

One patient randomised to placebo actually received VIR-7831 and is included in the safety data for the VIR-7831 arm but in the placebo arm for efficacy data. This patient had no AEs. One other patient was assigned an incorrect randomisation number but was not included in the ITT (IA) population because randomisation was after the ITT (IA) data cut. This patient was included in the Safety Population in the placebo arm, resulting in the SAF (IA) population comprising Placebo N=438 and VIR-7831 N=430. This patient had no AEs

Demographic, Baseline and disease Characteristics (SAF [IA])

Overall, baseline demographic and disease characteristics were well balanced between the treatment arms. Of the 868 patients, 53% were female. The median age was 53 years (range: 17-96) with 20% 65+years and 10% 70+ years. Overall, 65% of the patients were Hispanic or Latino (Table 27).

Table 27 – Summary of demographics characteristics at baseline (SAF) [IA]

Parameter	Placebo (N=438)	VIR-7831 500 mg (N=430)	Total (N=868)
Sex			
Male	212 (48%)	194 (45%)	406 (47%)
Female	226 (52%)	236 (55%)	462 (53%)
Age (Years)			
Mean (SD)	52.1 (14.79)	51.1 (14.84)	51.6 (14.81)
Median (Min, Max)[a]	52.0 (17, 88)	53.0 (18, 96)	53.0 (17, 96)
Age Group (Years)			
≤18	4 (<1%)	2 (<1%)	6 (<1%)
19 to 64	346 (79%)	344 (80%)	690 (79%)
≥65	88 (20%)	84 (20%)	172 (20%)
Age Group Strata (Years)			
≤70	396 (90%)	388 (90%)	784 (90%)
>70	42 (10%)	42 (10%)	84 (10%)
Ethnicity			
Hispanic or Latino	280 (64%)	280 (65%)	560 (65%)
Not Hispanic or Latino	158 (36%)	150 (35%)	308 (35%)
Race (high level)			
American Indian or Alaska Native	1 (<1%)	1 (<1%)	2 (<1%)
Asian	19 (4%)	21 (5%)	40 (5%)
Black or African American	33 (8%)	27 (6%)	60 (7%)
White	384 (88%)	374 (87%)	758 (88%)
Mixed Race	0	6 (1%)	6 (<1%)
Body Mass Index (BMI) (kg/m^2)			
Mean (SD)	32.5 (6.69)	32.0 (6.38)	32.3 (6.54)
Median (Min, Max)	31.9 (17.7, 71.2)	31.7 (14.3, 60.5)	31.8 (14.3, 71.2)

Interim Analysis 1 DCO: 04 March 2021

a. Age is imputed from year of birth. The calculation uses 30 June as the day and month and calculates age relative to Screening date. Participant(s) designated as "17" are a result of the calculation and not a protocol deviation.

The majority (85%) had a positive SARS-CoV-2 RT-PCR result based on local testing and the rest had a positive antigen test result. Available data show that baseline viral load was similar across treatment arms (Table 28). The three most common pre-defined risk factors or comorbidities in both treatment arms were obesity, 55 years of age or older and diabetes requiring medication. More than 99% had at least one risk factor associated with COVID-19 progression; obesity was the most common (Table 29).

Table 28 – Summary of SARS-CoV-2 test results at baseline (SAF [IA])

	Placebo (N=438)	VIR-7831 500 mg (N=430)	Total (N=868)
Positive Local SARS-CoV2 Test Result[a]			
Yes	438 (100%)	428 (>99%)	866 (>99%)
Missing	0	2 (<1%)	2 (<1%)
Specimen Type[a]			
n	438	428	866
Nasopharyngeal Swab	297 (68%)	270 (63%)	567 (65%)
Nasal Cavity Swab	126 (29%)	133 (31%)	259 (30%)
Oropharyngeal Swab	6 (1%)	13 (3%)	19 (2%)
Saliva	9 (2%)	10 (2%)	19 (2%)
Other	0	2 (<1%)	2 (<1%)
Method Diagnosis[a]			
n	438	428	866
RT-PCR	377 (86%)	360 (84%)	737 (85%)
Antigen	61 (14%)	68 (16%)	129 (15%)
Baseline SARS-CoV2 Viral Load (log10 copies/mL) in Nasal Secretions[b]			
n	201	184	385
Mean (SD)	6.494 (1.9170)	6.473 (1.8269)	6.484 (1.8721)
Median (Min, Max)	6.685 (3.047, 9.839)	6.622 (3.047, 9.985)	6.669 (3.047, 9.985)
<Lower limit of quantification (<2228 copies/mL)	11 (5%)	11 (6%)	22 (6%)
$\leq 10^5$	45 (22%)	30 (16%)	75 (19%)
$>10^5 - \leq 10^6$	24 (12%)	32 (17%)	56 (15%)
$>10^6 - \leq 10^7$	27 (13%)	32 (17%)	59 (15%)
$>10^7$	94 (47%)	79 (43%)	173 (45%)

Interim Analysis 1 DCO: 04 March 2021

a. SARS-CoV-2 diagnostic test results reflects point-of-care or local laboratory test at Screening, and not Baseline viral load at Day 1.
b. Central Nasopharyngeal Swab. Percentages based on population with detectable SARS-CoV-2 test value at Baseline in dataset available to date. Values less than the lower limit of quantification (LLQ) (LLQ=2228 copies/mL) have been imputed to 0.5 x LLQ prior to taking the log 10 value.

Table 29 – Summary of disease characteristics at baseline (SAF [IA])

	Placebo (N=438)	VIR-7831 500 mg (N=430)	Total (N=868)
Conditions as risk factor for COVID-19 progression[a]			
Any condition	434 (>99%)	427 (>99%)	861 (>99%)
Obesity (BMI >30 kg/m²)	292 (67%)	267 (62%)	559 (64%)
≥55 (Years)	205 (47%)	195 (45%)	400 (46%)
Diabetes requiring medication	88 (20%)	93 (22%)	181 (21%)
Moderate-to-severe asthma	72 (16%)	69 (16%)	141 (16%)
COPD	18 (4%)	24 (6%)	42 (5%)
Chronic kidney disease	5 (1%)	2 (<1%)	7 (<1%)
Congestive heart failure	3 (<1%)	4 (<1%)	7 (<1%)
Number of conditions met			
0	4 (<1%)	3 (<1%)	7 (<1%)
1	250 (57%)	251 (58%)	501 (58%)
2	130 (30%)	132 (31%)	262 (30%)
3	43 (10%)	38 (9%)	81 (9%)
>3	11 (3%)	6 (1%)	17 (2%)
Symptoms present (PI reported)			
Cough	359 (82%)	343 (80%)	702 (81%)
Muscle aches/Myalgia	312 (71%)	303 (70%)	615 (71%)
Headache	306 (70%)	298 (69%)	604 (70%)
Fatigue	258 (59%)	260 (60%)	518 (60%)
Sore Throat	244 (56%)	244 (57%)	488 (56%)
Malaise	238 (54%)	239 (56%)	477 (55%)
Loss of Taste	237 (54%)	234 (54%)	471 (54%)
Loss of smell	228 (52%)	237 (55%)	465 (54%)
Fever	231 (53%)	228 (53%)	459 (53%)
Joint pain/Arthralgia	227 (52%)	227 (53%)	454 (52%)
Chills	222 (51%)	226 (53%)	448 (52%)
Shortness of Breath	190 (43%)	176 (41%)	366 (42%)
Diarrhoea	155 (35%)	131 (30%)	286 (33%)
Nausea	120 (27%)	127 (30%)	247 (28%)
Vomiting	51 (12%)	47 (11%)	98 (11%)
Symptom duration (Days)			
n	438	428	866
≤3	260 (59%)	254 (59%)	514 (59%)
4-5	178 (41%)	173 (40%)	351 (40%)
>5	0	1 (<1%)	1 (<1%)

Interim Analysis 1 DCO: 04 March 2021

a. Medical Conditions present as risk factors at Screening for progression include: diabetes (requiring medication), obesity (BMI was amended under protocol amendment 1 from >30 to >35. Participants are only summarised in the BMI threshold under which they were screened), chronic kidney disease (i.e., estimated glomerular filtration rate [eGFR] <60 by Modification of Diet in Renal Disease [MDRD]), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion), and moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

Note: Participants may occur more than once in the list of risk factors and the list of symptoms present.

Current medical conditions at baseline and prior and concomitant medications (SAF [IA])

Overall, 2% of participants (VIR-7831: 3%; placebo: 1%) had received prior treatment for COVID-19. No single prior medication was noted in≥ 1% in either treatment arm. Prednisone therapy was documented in 4 and 0 participants (VIR-7831 and placebo, respectively).

The majority of the participants treated with VIR-7831 (88%) reported taking concomitant medications during the study. Steroid use was reported across the two treatment arms with dexamethasone being the most common (5% vs. 8%, in VIR-7831 and placebo arm, respectively). Concomitant ivermectin was noted for 10 (2%) participants in the placebo arm and 2 (<1%) in the VIR-7831 arm. Concomitant hydroxychloroquine was noted for 2 participants in each arm and convalescent plasma in 1 participant per arm (which represent protocol deviations). Concomitant remdesivir was administered to 3 (<1%) participants in the placebo arm that had progressed. Anti-infectives for systemic use were also balanced between both arms, with 59 (14%) participants in the VIR-7831 arm and 58 (13%) participants in the placebo arm.

Adverse events (AEs)

AEs reported as related to COVID-19 symptoms and COVID-19 progression were included. The overall rate of AEs was similar in those treated with VIR-7831 or placebo (VIR-7831: 73 [17%]; placebo: 85 [19%]). There were no differences between treatments in the frequency of AEs not related to COVID-19 (16% placebo: 16% VIR-7831) (Table 30). Supportive data from COMET-PEAK (PART-A), ACTIV-3-TICO and BLAZE-4 were limited but did not highlight any safety concern.

Table 30 – Adverse events overview in COMET-ICE (SAF [IA])

	Placebo (N=438)	VIR-7831 500 mg (N=430)
Any AE	85 (19%)	73 (17%)
AEs related to study treatment	8 (2%)	8 (2%)
AEs leading to permanent discontinuation of study treatment[a]	0	0
AE leading to dose interruption/delay	0	2 (<1%) [c]
Any Grade 3/4 AEs	27 (6%)	7 (2%)
Any SAE	26 (6%)	7 (2%)
SAEs related to study treatment	1 (<1%)	0
Fatal SAEs	2 (<1%)	0
Fatal SAEs related to study treatment	0	0
Any Infusion-Related Reactions including Hypersensitivity AESI[b]	5 (1%)	6 (1%)
IRRs related to study treatment	2 (<1%)	1 (<1%)
IRRs leading to permanent discontinuation of study treatment[a]	0	0
IRRs leading to dose interruption/delay	0	0
Interim Analysis 1 DCO: 04 March 2021		

a. A participant was permanently discontinued from the completion of drug infusion if they experienced life-threatening, infusion-related reactions, including severe allergic or hypersensitivity reactions during the IV infusion.

b. Infusion-related reactions (including hypersensitivity) are defined using a selection of preferred terms for AESIs that include pyrexia, chills, dizziness, dyspnoea, pruritus, rash, infusion-related reaction and only includes events that started within 24 hours of study treatment.

c. AEs leading to dose interruption were two events of infusion site extravasation. For both events, the infusion was able to be completed, and the time to complete the infusion was 1 h 17 min and 1 h, respectively.

Most common adverse events

Most AEs were more frequent in the placebo arm (Table 31). The exception was diarrhoea (6 [1%] VIR-7831: 3 [<1%] placebo). The six patients with AEs of diarrhoea in the VIR-7831 arm all had Grade 1 or Grade 2 events and five had resolved at the time of IA1 DCO. In addition, there was one event of worsening diarrhoea in the VIR-7831 arm but this was classified has Grade 1 and resolved.

Table 31 – Summary of adverse events in either treatment group (SAF [IA])

Preferred Term	Placebo (N=438)	VIR-7831 (500 mg IV) (N=430)
COVID-19 pneumonia[a]	14 (3%)	4 (<1%)
Headache	9 (2%)	3 (<1%)
Pneumonia	7 (2%)	0
Dehydration	5 (1%)	0
Dyspnoea	5 (1%)	2 (<1%)
Nausea	5 (1%)	4 (<1%)
Diarrhoea	3 (<1%)	6 (1%)

Interim Analysis 1 DCO: 04 March 2021

a As recorded by the investigator

The majority of non-serious AEs were Grade 1 or Grade 2 and a lower proportion in the VIR-7831 arm had DAIDs ≥Grade 3 AEs (2% vs. 6%). The types of DAIDs ≥Grade 3/4 AEs were typical of those seen in patients experiencing COVID-19.

Adverse events of special interest

Adverse events of special interest (AESIs) are defined as:

- Infusion-related reactions (IRR) including serious hypersensitivity reactions; reactions within 24 hours of infusion
- Adverse events potentially related to immunogenicity
- Adverse events potentially related to antibody-dependent enhancement of disease

A custom list of MedDRA terms was used to identify AESIs based on review of PTs in the standardised MedDRA query for hypersensitivity reactions and anaphylactic reactions, encompassing hypersensitivity, angioedema, anaphylaxis, acute anaphylactic shock and minor allergic episodes as per protocol. Infusion-related reactions included a selection of AEs with PTs such as pyrexia, chills, dizziness, dyspnoea, pruritus, rash or infusion-related reaction.

Systemic infusion-related reactions were observed with similar frequency with VIR-7831 (6/430 [1%]) or placebo (5/438 [1%]). All IRRs were Grade 1 or 2 and clinically manageable with no life-threatening reactions. AEs leading to dose interruption were two events of infusion site extravasation in the VIR-7831 arm. For both events, the infusion was completed and the times to complete the infusion were 1 h 17 min and 1 h, respectively. Reported IRRs that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnoea, pruritus, rash, and infusion-related reaction: all events were Grade

1 or 2. As of the data cut-off, half of the cases in VIR-7831 arm were noted to have been resolved, 2 had not resolved and 1 was resolved with sequelae. There were no reports of serious hypersensitivity reactions such as anaphylaxis following infusion with VIR-783.

Frequency of IRRs by System Organ Class and Preferred Term (SAF [IA])

Preferred Term	Placebo (N=438)	VIR-7831 500 mg (N=430)
Any event	5 (1%)	6 (1%)
General disorders and administration site conditions		
Any event	1 (<1%)	4 (<1%)
Pyrexia	1 (<1%)	3 (<1%)
Chills	0	2 (<1%)
Nervous system disorders		
Any event	2 (<1%)	1 (<1%)
Dizziness	2 (<1%)	1 (<1%)
Skin and subcutaneous tissue disorders		
Any event	2 (<1%)	0
Pruritus	1 (<1%)	0
Rash	1 (<1%)	0
Injury, poisoning and procedural complications		
Any event	0	1 (<1%)
Infusion-related reaction	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders		
Any event	1 (<1%)	1 (<1%)
Dyspnoea	1 (<1%)	1 (<1%)

Interim Analysis 1 DCO: 04 March 2021
Source: Table 3.6

The ADA assays have recently been validated (screening, confirmatory and titre assays). The ADA incidence and the effect of ADA after a single dose of VIR-7821 on PK, efficacy and safety are currently unknown. Also, VIR-7831 will be given as a single-dose treatment. Further data are awaited.

No events consistent with ADE were detected by the Safety Review Team (blinded review) or the Independent Data Monitoring Committee (unblinded review).

Deaths

As of IA1 DCO (04 March 2021), no deaths were reported in the VIR-7831 treatment arm. Two deaths were reported in the placebo arm due to COVID-19 pneumonia, one on Day 20 and one on Day 37.

List of Deaths (SAF [IA])

Participant identifier	Sex (M/F)/ Age (years)/ Race	Days from dose to onset of fatal AE	Days from dose to death	Adverse event (preferred term)	AE possibly causally related to study drug?	Primary cause of death[a]	Death related to disease under investigation (per PI)?[a]	Relevant Medical History
Placebo								
10513	M/70/Caucasian	4	20	Pneumonia	No	COVID pneumonia	Yes	History of asthma, chronic bronchitis, COPD, emphysema, lung infection with upper lobe lobectomy and obesity
11621	F/71/Caucasian	8	37	COVID-19 pneumonia	No	COVID pneumonitis	Yes	Obesity

Interim Analysis 1 DCO: 04 March 2021
Source: Listing 3 and Listing 10
a. data derived from CIOMS

Serious Adverse Events

SAEs due to progression of COVID-19 are also included in the SAE summaries (Table 32).
The majority of SAEs not related to the progression of COVID-19 occurred in the placebo arm (3% placebo: 1% VIR-7831). Serious AEs were reported in 7 of 430 (2%) of participants in the VIR-7831 arm compared to 26 of 438 (6%) of participants in the placebo arm.

Table 32 – Serious adverse events overview (SAF [IA])

System Organ Class Preferred Term	Placebo (N=438)	VIR-7831 500 mg (N=430)
Number of Participants with SAEs	26 (6%)	7 (2%)
Number of SAEs	30	8
Number of Participants with Fatal SAEs	2 (<1%)	0
Number of Participants with Treatment-Related SAEs	1 (<1%)	0

Interim Analysis 1 DCO: 04 March 2021

The 7 SAEs in 7 patients treated with VIR-7831 are shown below.

Table 33 - Listing of serious adverse events (SAF [IA]

Participant identifier	Sex (M/F)/ Age (years)/ Race	Days to SAE from dose	Serious Adverse Event (preferred term)	SAE possibly causally related to study drug? (per PI)	SAE related to disease under investigation (per PI)?[a,b]	Relevant Medical History
VIR-7831						
10509	F/80/Caucasian	90	Diverticulitis	No	N/S	History of diverticulitis
10808	M/31/Caucasian	50	Diverticulitis	No	N/S	History of diverticulitis
11630	F/31/Caucasian	5	Diabetes mellitus	No	N/S	History of diabetic ketoacidosis
13008	F/71/Caucasian	1	COVID-19 pneumonia	No	Yes	
13055	M/57/Caucasian	13	Hyperglycaemia Non-small cell lung cancer	No	N/S	Insulin-dependent diabetes, hyperlipidemia, obesity; and 120 pack-years smoking history
12202	F/65/Caucasian	22	Small intestinal obstruction	No	N/S	History of small bowel obstruction
11905	M/96/Caucasian	19	COVID-19	No	Yes	-

Interim Analysis 1 DCO: 04 March 2021
Source: Listing 3 and Listing 12
a. data derived from CIOMS
b. N/S denotes not specified in the PI narrative

Single reports of the following SAEs were noted in the placebo arm: acute respiratory failure, acute kidney injury, dyspnoea, hypoxia, hypovolaemia, obstructive pancreatitis, oxygen saturation decreased, pulmonary embolism and respiratory distress. One SAE (COVID-19 pneumonia), which occurred in a placebo group patient, was considered to be possibly related to study drug by the investigator.

Immunogenicity

At the time of IA1 DCO (04 March 2021), no immunogenicity data were available from the COMET-ICE study. The ADA incidence and the effect of ADA after a single dose of VIR-7821 on PK, efficacy and safety are currently unknown. The ADA assays have recently been validated (screening, confirmatory and titre assays). Assays to characterise the activity of potentially neutralising ADA (NAb) in participant serum samples are under development. Method qualification and validation are not yet available.

Antibody Dependent Enhancement (ADE)

No events consistent with ADE were observed.

Safety in special populations

Fertility, Pregnancy and Lactation

There were no pregnancies reported in the submitted data. No clinical data on human fertility, pregnancy or lactation is available. Human immunoglobulin G (IgG) as VIR-7831 can potentially pass the placental barrier from mother to foetus. Human IgGs are known to be excreted in breast milk.

Elderly

Adverse events (AEs) for participants who were <65 years and ≥65 years of age are presented in table 34. The overall rate of non-serious AEs was slightly higher in the ≥65 years subgroup than in the <65 years subgroup in both the placebo (23% vs 19%) and sotrovimab treatment arms (20% vs 16%). Regardless of age subgroup, the overall rate of AEs was slightly higher in the placebo arm as compared to the sotrovimab arm.

The overall rate of serious adverse events (SAEs) was higher in the ≥65 years subgroup than in the <65 years subgroup in both the placebo (13% vs 4%) and sotrovimab (5% vs <1%) treatment arms.

Table 34 - Summary of Adverse Events and Serious Adverse Events by Age (<65, ≥65 years) (Amended SAF [IA])

System Organ Class Preferred Term	Placebo (N=437)	Sotrovimab (500 mg IV) (N=431)
Number of Adverse Events		
<65 years	65 / 349 (19%)	56 / 347 (16%)
≥65 years	20 / 88 (23%)	17 / 84 (20%)
Number of Serious Adverse Events		
<65 years	15 / 349 (4%)	3 / 347 (<1%)
≥65 years	11 / 88 (13%)	4 / 84 (5%)

Interim Analysis 1 DCO: 04 March 2021

Table 35 shows the AEs reported in ≥1% of participants in either treatment arm in the SAF (IA) population presented by age (<65 years vs ≥65 years). Of these, most events occurred more frequently in the placebo arm; the sole exception was diarrhoea (<1% placebo, 1% sotrovimab) in the <65 age group. Of note, the 3 events of COVID-19 pneumonia represented all 3 progressions in the sotrovimab arm.

Table 35 - Summary of Adverse Events (≥1%) in Either Treatment Group (Amended SAF [IA]) by Age (<65, ≥65 years)

Preferred Term	Placebo (N=437)		Sotrovimab (500 mg IV) (N=431)	
	Age		Age	
	<65 Years	≥65 Years	<65 Years	≥65 Years
Number of Participants	349	88	347	84
COVID-19 pneumonia	11 (3%)	3 (3%)	1 (<1%)	3 (4%)
Headache	8 (2%)	1(1%)	2 (<1%)	1 (1%)
Pneumonia	4 (1%)	3 (3%)	0	0
Dehydration	3 (<1%)	2 (2%)	0	0
Dyspnoea	4 (1%)	1 (1%)	2 (<1%)	0
Nausea	4 (1%)	1 (1%)	3 (<1%)	1 (1%)
Diarrhoea	2 (<1%)	1 (1%)	5 (1%)	1 (1%)

Interim Analysis 1 DCO: 04 March 2021

Laboratory findings

Emergent Severe Laboratory Abnormalities

Overall, 21 (4.8%) in the VIR-7831 treatment arm and 9 (2%) in the placebo arm had laboratory results with Grade 3 or higher DAIDS values outside of the normal range for clinical chemistry parameters. Overall, 27 had worsening renal laboratory abnormalities that were categorised as severe (Grade 3) and 2 (both in the placebo group) had potentially life-threatening (Grade 4) laboratory abnormalities (these were also reported as Grade 4 AEs).

Among the patients with Grade 3 and 4 creatinine shifts, many in both arms had isolated increases in creatinine values that reverted to normal/near normal values during subsequent evaluations. In several others there was an isolated increase at the last available laboratory visit. There was no difference in mean change from baseline in creatinine between the placebo and VIR-7831 arms.

To date, one patient in the VIR-7831 arm has had Grade 3-4 transaminase elevations. The patient was a 50-year-old female with a history of obesity, diabetes, high cholesterol, COPD and chest tightness. The patient had Grade 1 AEs of fever, chills and diarrhoea on Day 1 with baseline Grade 1 elevations in AST and ALT. The patient developed Grade 3 elevations in AST and ALT on Day 22. On Day 29, the ALT had increased while the AST had decreased but both were elevated at Grade 3. The patient is being followed up.

Clinical Chemistry – Overall and Maximum DAIDS Grade 3/4 Shift (SAF [IA])

	Placebo N=438		VIR-7831 500 mg N=430	
Laboratory Parameter	Any grade shift n (%)	Grade 3/4 shift n (%)	Any grade shift n (%)	Grade 3/4 shift n (%)
ALT/ALT or SGPT, high[a]	32 (9%)	0	29 (8%)	1 (<1%)[a]
AST/AST or SGOT, high[a]	18 (5%)	0	9 (2%)	1 (<1%)[a]
Creatinine/Creatinine, high	39 (11%)	9 (2%)	50 (13%)	20 (5%)
Potassium/Potassium, high	6 (2%)	0	5 (1%)	0
Potassium/Potassium, low	6 (2%)	0	2 (<1%)	0
Total Bilirubin/Total Bilirubin, high	3 (<1%)	0	4 (1%)	0

Interim Analysis 1 DCO: 04 March 2021
Source: Table 3.14
n = number of participants with results post-baseline
a Both ALT and AST grade shifts were reported in participant 013403.

One patient in the VIR-7831 arm and 3 in the placebo arm had 4 laboratory results with Grade 3 DAIDS values for haematology parameters. Of these Grade 3 changes, a shift in haemoglobin occurred in a VIR-7831 patient with an ongoing history of gout, obesity, diabetes mellitus and hypertension. The haemoglobin on Day 1 was 9.2 g/dL (normal range: 12.7-18.1 g/dL).

	Placebo N=438		VIR-7831 500 mg N=430	
Laboratory Parameter	Any grade shift n (%)	Grade 3/4 shift n (%)	Any grade shift n (%)	Grade 3/4 shift n (%)
Haemoglobin/Haemoglobin, low	19 (6%)	0	12 (4%)	1 (<1%)
Lymphocytes/Absolute Lymphocyte Count, low	6 (2%)	3 (<1%)	1 (<1%)	0
Neutrophils/Absolute Neutrophil Count (ANC), low	0	0	2 (<1%)	0
Platelets/Platelets, decreased	3 (<1%)	0	2 (<1%)	0
White Blood Cell count/WBC, decreased	2 (<1%)	0	1 (<1%)	0

Interim Analysis 1 DCO: 04 March 2021
Source: Table 3.15

Vital Signs including electrocardiograms

Changes in the mean systolic and diastolic blood pressure, the mean pulse rate, mean respiratory rate and temperature between baseline and Day 29 were minor generally similar across treatment arms. 12-lead ECGs were obtained at baseline and daily for 8 days for patients in the Lead-in phase. No significant ECG findings related to VIR-7831 was reported in COMET-ICE study, as of IA1 DCO (04 March 2021).

Safety data from other studies

Safety data (blinded or unblinded) are presented for 700 patients (hospitalised and non-hospitalised) who received VIR-7831 IV in clinical trials.

COMET-PEAK (PART-A)
As of 18 March 2021, 5 patients have received VIR-7831 and no SAEs have been reported.

ACTIV-3-TICO

As of 23 February 2021, 344 patients had been randomised: 169 to Group A (VIR-7831) and 175 to Group B (placebo). There were no safety concerns identified by the DSMB. In total, 14 had died, with 8 in the VIR-7831 group and 6 in the placebo group. All except one death occurred after Day 5 and all deaths were attributed to COVID-19 except one in the VIR-7831 group reported as multiple organ dysfunction syndrome (MODS) on Day 19 in a 61-year-old female with baseline oxygen requirement >4 L/min. The patient had respiratory failure at baseline, a serious co-infection on Day 4, hypotension and Grade 4 septic shock on Day 7, renal dysfunction on Day 16, hepatic dysfunction on Day 17 and a thromboembolic event and cerebrovascular event on Day 18. The MODS was assessed by the investigator as unrelated to COVID-19 but causality to study treatment was not provided.

SAEs were reported for 6 (3.6%) in the VIR-7831 group (see table below) and 8 (4.6%) in the placebo group. Conditions known to occur as complications of COVID-19 were not reported as SAEs (unless judged to be related to the study treatment) but were collected separately as clinical organ failure and serious infections. There was no evidence of a treatment difference in rates of clinical organ failure or serious infections, including rates of respiratory failure.

Table 36 – List of serious adverse events reported in VIR-7831 arm of supportive studies

Participant identifier/ Treatment	Sex (M/F)/ Age (years)/ Race	Time/Days to SAE from dose start	Adverse Event (preferred term)	SAE possibly causally related to study drug (per PI)?	SAE related to disease under investigation (per PI) [a]?	Narrative summary
COMET-PEAK (Part-A) (DCO: 18 March 2021)						
None						
ACTIV-3-TICO (DCO: 23 February 2021) Unblinded						
140-4281-6 VIR-7831	F/92	~21 min	Anaphylaxis	Yes	No	Medical history of hypertension, anxiety, and depression. No reported history of allergies. Experienced symptoms including worsening shortness of breath and chest tightness associated with flushing, expiratory wheezing, and skin rash leading to premature permanent discontinuation of infusion after ~20 min. Treatment included IM epinephrine, H1/H2 blockade with improvement. 2nd recurrence 2 hours later which improved with similar treatment. Tryptase 12.5 ng/mL (ULN 11.5). Brighton's anaphylaxis Level 1 criterion met.
140-4294-9 VIR-7831	M/86	~2 h	Cytokine release syndrome (CRS)	Yes	No	Medical history of coronary artery disease, hypertension, and ankylosing spondylitis. 3 hours post infusion, developed new onset shortness of breath, fever, shaking chills, diaphoresis, dyspnoea, tachypnoea, tachycardia, nausea, and vomiting which improved following treatment with IV Benadryl and Pepcid. There were no protocol-defined criteria for cytokine release syndrome and no serum cytokines were assessed. No epinephrine was needed.
140-3653-7 VIR-7831	M/74	~4 h	Respiratory failure	No	Yes	Multiple baseline risk factors for COVID progression including obstructive sleep apnoea on CPAP, COPD, insulin-dependent diabetes, CKD stage 4 (baseline creatinine 1.7-2 mg/dL), asbestos lung disease. Participant had been hospitalised for progressive hypoxemia requiring additive oxygen support in ER, and with ICU admission being contemplated at the time before randomisation to VIR-7831 infusion. Infusion was without incidence; however, 4 hours later, participant had progressive O_2 desaturation and worsened CXR leading to ICU transfer and intubation.
140-4540-5 VIR-7831	M/58	~4 h	Respiratory distress	Yes	Yes	Multiple baseline risk factors for COVID progression including end stage renal disease on dialysis, coronary artery disease, Type 2 diabetes and congestive heart failure. Approximately 9 days after COVID diagnosis, patient hospitalised for progressive hypoxemia, fevers and rigors with multifocal bilateral ground glass and consolidative opacities on chest CT. Baseline C-reactive protein rose from 24.8 mg/L to 30.5 mg/L. Participant was on 4L NC O_2 at time of infusion and tolerated infusion without incident. 4 hours post infusion he had recurrence of fever with tachycardia and O_2 desaturation with worsened CXR findings eventually leading to ICU transfer and intubation.

Participant identifier/ Treatment	Sex (M/F)/ Age (years)/ Race	Time/Days to SAE from dose start	Adverse Event (preferred term)	SAE possibly causally related to study drug (per PI)?	SAE related to disease under investigation (per PI) [a]?	Narrative summary
140-4307-9 VIR-7831	F/50	21 days	Hypercalcemia	No	Yes	No medical history provided. Participant received infusion without incident. Had a creatinine level of 0.7 µmol/L (normal range not provided) at discharge. Rehospitalised 22 days later due to dyspnoea and palpitations. Calcium level noted to be elevated at 11.4 mg/dL(normal range not provided); however, parathyroid hormone and Vitamin D levels were normal. Chest x-ray showed multifocal ground glass opacities and bronchial thickening. ECG did not reveal any ischemic changes and troponins remained negative. Calcium improved following volume resuscitation (Calcium 8.4 mg/dL) at time of discharge. Suspected hypercalcemia due to dehydration.
140-4233-7 VIR-7831	F/57	1 day	Hypoxia	No	Yes	Participant was enrolled in the ACTIV-3 study on 02 February 2021. The participant was discharged on 02 February 2021 after receiving study medication on 3L of oxygen via nasal cannula. Participant presented to the study hospital the following day, after becoming more hypoxaemic and requiring 6L of oxygen via nasal cannula. According to the Investigator, the participant's presentation is most consistent with progression of worsening coronavirus in the setting of new oxygen requirement with known coronavirus infection.
BLAZE-4 (DCO: 04 March 2021)						
None						

[a] N/S denotes not specified in the PI narrative provided

Two patients in the VIR-7831 group had at least one Grade 4 IRR:

- A 92-year-old female in the VIR-7831 group experienced Grade 4 anaphylaxis and bronchospasm, Grade 3 shortness of breath, Grade 2 rash, and Grade 1 dizziness and flushing 21 minutes after the start of the infusion, which was stopped. Epinephrine was given and the event resolved.
- A 75-year-old male in the VIR-7831 group experienced Grade 4 shortness of breath within 4 hours after the start of the infusion. This infusion reaction was reported as an SAE and was described as respiratory failure.

One patient in the placebo group experienced a Grade 4 IRR.

Grade 3/4 AEs were collected through Day 28. The hazard ratio for the composite outcome of Grade 3 or 4 AEs, SAEs, organ failure, serious infections or death favoured VIR-7831 group (HR=0.79 [95% CI: 0.51 to 1.23; p=0.30]).

There was no evidence for differences between the groups in the Day 5 laboratory data or any evidence for a difference in the frequency of Grade 3 or 4 laboratory toxicities between the 2 groups.

BLAZE-4

In the BLAZE-4 study, 206 patients were randomised to receive VIR-7831 in combination with bamlanivimab (101) or placebo under blinded conditions. Enrolment completed on 05 February 2021.

Bamlanivimab and VIR-7831 were infused sequentially, each given over 30 minutes with a 30-minute interval. No SAEs or IRRs have been reported. Patients will continue to be followed for 24 weeks.

2.2.5. Conclusions on safety

In COMET-ICE, safety data are reported for 868 patients with a median duration of follow-up of 56 days (range 5-190). Of the 868, 747 were followed through >29 days and 18 of these had been followed for 24 weeks. Supportive safety data on approximately 270 participants having received VIR-7831 as part of ongoing clinical trials investigating VIR-7831 as monotherapy or in combination with bamlanivimab were included. In the COMET-ICE study, diaries were used for solicited adverse events,

whereas unsolicited adverse events were collected by communication with the participant and reported in eCRF's. Instruments for PROM (Flu-PRO Plus) or QoL were not used to capture adverse events. At present, results from FLU-Pro plus and the questionnaires are not reported, which is not critical for the current Article 5(3) procedure.

No major safety concerns have been identified for the use of VIR-7831 in the target population. Infusion-related reactions can occur with humanised monoclonal antibodies, some of which may be severe so that vigilance is needed during and for a while after the infusion. Anaphylaxis has been reported with VIR-7831, which is not unexpected. Patients were observed for 2 hours after the infusion was completed. As there has not been identified any increase in risk of infusion related reactions or anaphylaxis compared to other monoclonal antibodies monitoring for 1 hour after infusion is considered adequate.

Of the AEs reported in ≥1% of patients, diarrhoea was the only AE reported more frequently with VIR-7831 (6 [1%] vs. 3 [<1%] placebo). The applicant has listed the 7 most common AEs in the draft Conditions for Use rather than ADRs. According to the data submitted, 8 patients (2%) in each treatment group had an AE considered related to treatment, none of which in the VIR-7831 group was a SAE. One AE in the VIR-7831 group and 2 in the placebo group were treatment-related infusion reactions. However, no tabulation of ADRs have been submitted in this procedure. As the number is considered low and as none of the drug related reactions are severe, this is considered acceptable in the context of this Article 5(3) procedure. However, further details on ADRs should be provided within the appropriate framework.

The overall frequency of AE was higher in participants older than 65 years; however, the frequency was higher in the placebo group compared with VIR-7831 for both AE and SAE. For the 1% most frequent adverse events in participants older than 65 years, COVID-19 pneumonia occurred in 4% (3 participants) in VIR-treated participants and in 3% (3 participants) in the placebo arm. As VIR-7831 is expected to have an effect on COVID-19 pneumonia, it is surprising that no difference in COVID-19 pneumonia is observed among participants older than 65 years. This is not pursued further for this 5(3) procedure but should be further addressed within the appropriate framework.

No immunogenicity data are available at present. However, since VIR-7831 is intended to be given once, ADA is not considered a concern by CHMP.

Vaccine with any COVID-19 vaccine was not allowed prior to inclusion in the study. Therefore, the risk of treating break through cases with VIR-7831 is unknown.

The safety data of VIR-31 in special populations including pregnant women and immunocompromised patients is scarce. No pregnancies were reported in the submitted data and severely immunocompromised participants were excluded from participating in the study.

Although CHMP recognized the limitations of the available safety database, in the context of this Article 5(3) procedure it is considered to be sufficient to support the use of sotrovimab in an emergency setting.

2.3. Non-clinical aspects

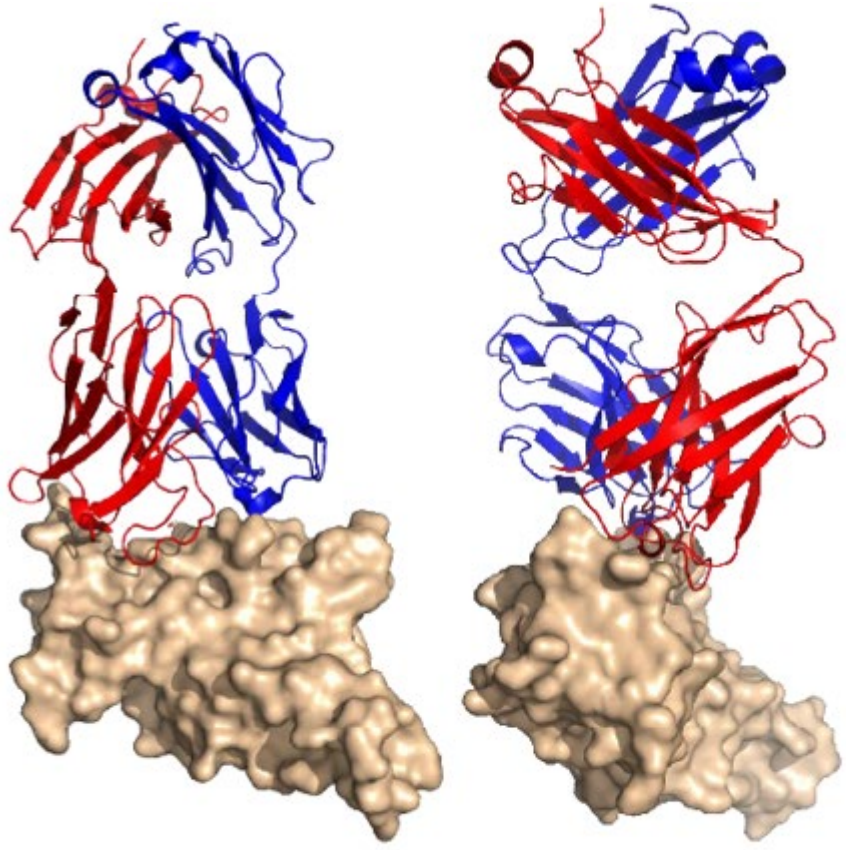
GSK4182136 has undergone a targeted programme of nonclinical pharmacology, pharmacokinetic (PK)/toxicokinetic (TK) and toxicology studies to support the development and forthcoming MAA of GSK4182136. The nonclinical programme was designed in accordance with the guidance provided in ICH S6(R1) and other applicable guidance as pertaining to a non-endogenous antiviral target.

Pharmacology

GSK4182136 is a human IgG1 mAb that binds to a highly conserved epitope on the spike (S) protein RBD of SARS-CoV-2 with high affinity (dissociation constant Kd = 0.21 nM). GSK4182136 was derived from the parent mAb S309 which was isolated from a SARS CoV-1 survivor [Pinto, 2020[3]]. GSK4182136 targets a highly conserved, unique receptor-binding domain epitope shared by SARS-CoV and SARS-CoV-2 distinct from the receptor-binding motif. See figure 4 below.

GSK4182136 (also known as VIR-7831) is a is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) which includes a 2 amino acid "LS" modification in the Fc domain of the antibody to extend its's half-life. This "LS" modification is also reputed to enhance distribution to the respiratory mucosa. GSK4182136 targets the spike protein of SARS-CoV-2 and was derived from the parental mAb S309, which was originally identified from a SARS-CoV infected survivor. The proposed mechanism of action is through its ability to target the spike protein of SARS-CoV-2, GSK4182136 will suppress viremia and accelerate clearance of infected cells.

Figure 4 – Crystal structure of SARS-CoV-2 RBD in complex with S309 Fab



Crystal structure of the SARS-CoV-2 RBD-S309 Fab complex (S304 omitted for clarity). The Fab is shown as a ribbon diagram (heavy chain in red, light chain in blue) and the RBD as a surface representation (tan). The right panel is a 90° rotation of the left panel.

[3] Pinto D, Park YJ, Beltramello M, Walls AC, Tortorici MA, Bianchi S, Jaconi S, Culap K, Zatta F, De Marco A, Peter A, Guarino B, Spreafico R, Cameroni E, Case JB, Chen RE, Havenar-Daughton C, Snell G, Telenti A, Virgin HW, Lanzavecchia A, Diamond MS, Fink K, Veesler D, Corti D. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature. 2020 Jul;583(7815):290-295. doi: 10.1038/s41586-020-2349-y. Epub 2020 May 18. PMID: 32422645.

In vitro

Binding studies

The binding activity of GSK4182136 to the SARS-CoV-2 spike protein was determined and a half maximal effective concentration (EC_{50}) value of 20.40 ng/mL calculated using an enzyme-linked immunosorbent assay (ELISA) to the spike monomer protein. An equilibrium constant (K_D) of 0.21 nM was measured by surface plasmon resonance to a recombinant RBD domain of the spike protein. In addition, flow cytometry was utilised to detect binding of GSK4182136 to cell surface-expressed SARS-CoV-2 spike protein trimer.

Neutralisation of SARS-CoV-2

The neutralising capacity of GSK4182136 was evaluated against SARS-CoV-2 virus using a VeroE6 cell-based system. Concentration-dependent viral neutralisation was observed, with an average EC_{50} value of 100.1 ng/mL (range: 76.6 – 132.5 ng/mL) and an average EC_{90} value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL). Using a vesicular stomatitis virus (VSV)-based pseudotyped virus system viral neutralisation the calculated EC_{50} value was 24.06 ng/mL (range: 20.56-28.60 ng/mL) and EC_{90} value of 107.72 ng/mL (range: 83.37-144.7 ng/mL). An analysis of spike protein coding sequences was used to identify prevalent variants (at the time of analysis in May 2020). GSK4182136 neutralized SARS-CoV-2 pseudotyped viruses with all variants EC_{50} values within < 2-fold change in EC_{50} relative to wild type. The highly prevalent D614G variant, either alone or in combination, did not alter neutralisation activity. In addition, GSK4182136 activity was tested against emerging spike variants including the United Kingdom (UK) variant B.1.1.7, South Africa (SA) variant B.1.351, Brazil variant P.1 and California variant CAL.20C. Fold-changes in EC_{50} ranged from 0.35- to 2.30-fold indicating that VIR-7831 remains active against these spike variants in this test system.

Table 37 - Susceptibility of Pseudovirus B.1.1.7, B.1.351, P.1 and CAL.20C Spike Variants to GSK4182136 *in vitro*

SARS-CoV-2 Variant Name	Variants in Tested Spike Sequence	VIR-7831 EC_{50} (ng/ml)	Average Fold Change in EC_{50} Compared to Relative Wild-Type[a]
B.1.1.7 (UK)	H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	223.04	2.30
B.1.351 (SA)	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V	60.18	0.60
P.1 (Brazil)	D138Y, D614G, E484K, H655Y, K417T, L18F, N501Y, P26S, R190S, T1027I, T20N, V1176F	29.58	0.35
CAL.20C (California)	D614G, L452R, S13I, W152C	58.23	0.70

Geomean = geometric mean
[a] Wild type sequence YP_009724390.1
Source: PC-7831-0123

Epitope mapping

Epitope mapping was performed to identify the amino acid residues of the SARS-CoV-2 spike protein to which GSK4182136 binds. The identified epitope comprises 22 amino acids and is distinct from the receptor binding motif, the site on the RBD where angiotensin converting enzyme 2 (ACE2) binds to facilitate entry for SARS-CoV-2 into cells. An analysis of the GISAID database suggested that the amino acids in the epitope were highly conserved with ≥99.97% conservation amongst the available sequences. To evaluate the epitope variant susceptibility to GSK4182136, amino acid substitutions were introduced into the SARS-CoV-2 spike coding sequence and assessed in a SARS-CoV-2 pseudotyped virus neutralisation assay. Variants at two positions, E340 and P337, resulted in significant EC_{50} shifts indicating reduced susceptibility to GSK4182136. Moderate shifts in potency were observed for P337H and P337T variants (7.50- and 5.38-fold, respective) while more significant shifts in potency were observed for P337L/R and E340A/K/G (27-fold to >297-fold).

Table 38 - Neutralisation Activity of GSK4182136 Spike Variants in SARS-CoV-2 Pseudotyped Virus

Epitope Reference Amino Acid	Amino Acid Changes in Spike protein	Geomean Neutralization EC_{50} (ng/mL)	Average Fold-Change EC_{50} Relative to Wild-Type[b]
N334	N334K, D614G	45.36	1.27
L335	L335F	29.19	0.81
P337	P337H, D614G[a]	225.49	7.50
	P337L, D614G[a]	5241.44	180.46
	P337R, D614G[a]	>10000	>276
	P337S, D614G	127.69	1.26
	P337T, D614G[a]	199.78	5.38
G339	G339D, D614G	117.38	1.18
E340	E340A	>10000	>100
	E340K	>10000	>297
	E340G, D614G[a]	1013.97	27.47
V341	V341I, D614G	14.60	0.16
A344	A344S	92.19	0.89
R346	R346K, D614G	24.76	0.72
N354	N354D	104.80	1.00
	N354K, T95I	70.62	0.76
	N354S, D614G	61.78	0.89
S359	S359N	95.55	0.96
N440	N440K, D614G	19.99	0.48

Geomean = geometric mean
[a] Variants were tested using the VIR-7831 parent antibody S309.
[b] Wild type sequence YP_009724390.1
Source: PC-7831-0124

In Vitro Resistance Barrier Assessment

The potential to select SARS-CoV-2 Variants in the presence of GSK4182136 was assessed using a surrogate antibody, VIR-7832 which contains a "XX2" modification in the Fc domain but with identical Fab regions. SARS-CoV-2 was subjected to 10 passages in the presence of VIR-7832 at fixed concentrations of ~10X, 20X, 50X or 100X EC_{50} in VeroE6 cells. No detectable virus was observed at any concentration of VIR-7832 through all 10 passages suggesting a high barrier to resistance in vitro. A similar study performed where the virus was initially passaged in sub-EC_{50} concentrations of

antibody, followed by subsequent passaging in increasing concentrations of mAb for up to 8 passages. Viral passages where a shift in neutralisation (>2-fold relative to wild type) was detected were subjected to RNA isolation and subsequent sequence analysis of the spike gene (Table 39).

Table 39 - Amino Acid Substitutions Identified in Spike Gene of SARS-CoV-2 in the Presence of VIR-7832

Passage	Spike Gene Amino Acid Substitution (Freq) [a,b]	EC_{50} (µg/mL)	Fold Change in EC_{50} to WT[c]
SARS-CoV-2 virus stock[c]	H66R (5.7%) N74K (12.6%) T76I (5.6%) 215-216insKLRS (60.9%) H655Y (3.1%)	0.06	NA
VIR-7832 Lineage 1, passage 4	215-216insKLRS (74.5%) 675-679 del (20.6%)	0.34	5.64
VIR-7832 Lineage 1, passage 5	215-216insKLRS (74.6%) 675-679del (66.0%)	0.35	5.93
VIR-7832 Lineage 1, passage 8	215-216insKLRS (74.7%) E340A (98.7%) 675-679del (84.5%)	ND	>10
VIR-7832 Lineage 2, passage 5	215-216insKLRS (73.9%) 675-679del (47.3%) R682W (4.9%) V1128F (3.5%)	0.32	5.40
VIR-7832 Lineage 2, passage 6	215-216insKLRS (75.3%) 675-679del (74.2%) R682W (4.9%) V1128F (30.9%)	0.39	6.54

Del = deletion; freq = frequency; ins = insertion; NA = not applicable; ND = not determined; WT = wild type
[a] Spike gene sequences were compared to a SARS-CoV-2 reference sequence (NCBI: NC_045512.2) to call variants
[b] Sequence changes are reported for the SARS-CoV-2 input virus. EC_{50} values and fold changes were determined for the SARS-CoV-2 virus stock.
[c] Fold change EC_{50} values were compared to SARS-CoV-2 virus stock
Source: PC-7831-0109

The effect of the identified amino acid substitutions in the resistance selection studies was tested by examining GSK4182136 binding to cell surface expressed full length spike protein containing the variants. GSK4182136 bound to the wild type SARS-CoV-2 spike protein, as well as to spike protein encoding mutations R682W and V1128F, but demonstrated reduced binding activity to E340A. In follow-up neutralisation assays using a SARS CoV 2 pseudotyped virus the EC50 values using GSK4182136 were similar to wild type for mutations R682W and V1128F, however, E340A conferred reduced susceptibility to VIR-7831 (> 100-fold change in EC_{50}) indicating that E340A is a monoclonal antibody resistance mutant (MARM). Available SARS-CoV-2 spike sequences deposited in the GISAID database were analysed. The selected variants R682W and V1128F were detected in ≤0.004% of sequences. E340A was not detected, however, the E340K variant was detected in 5 sequences of > 116,000 (0.004%). The ability of GSK4182136 to bind and neutralise the E340K variant is currently being tested.

Cross-resistance to SARS-CoV-2 monoclonal antibody resistance mutations (MARMs) that confer reduced susceptibility to other monoclonal antibody agents, bamlanivimab, casirivimab and/or imdevimab, was assessed. Fold changes in EC_{50} values compared to wild-type were <3-fold for 18/19

variants tested. A modest 3.38-fold shift in the VIR-7831 EC_{50} was observed for the V445A variant that confers reduced susceptibility to imdevimab.

In Vitro Effector Function Studies

Fc-dependent mechanisms of action mediated by the interaction of the Fc region with FcγRs on immune cells, or with complement, can potentially also make important contributions to overall potency. GSK4182136 bound both the H131 and R131 alleles of FcγIIa, FcγIIb and both the F158 and V158 alleles of FcγRIIIa. In addition, GSK4182136 bound the complement component C1q. The functional activity of activation of FcγRs by GSK4182136 was demonstrated using a surrogate assay for ADCC signalling. Lower activation of FcγRIIIa F158 versus V158 was seen which is characteristic for human IgG1. These data demonstrate that GSK4182136 activates antibody mediated effector functions in vitro.

ADCC and ADCP assays were performed using CHO cells stably transfected with SARS-CoV-2 spike protein (CHO-CoV-2-Spike) as target cells. To assess ADCC freshly isolated human NK cells were used. GSK4182136 induced NK cell-mediated ADCC when using cells from either F/F158 (low-affinity) or V/V158 (high-affinity) donors. ADCP was assessed using freshly isolated human PBMCs where GSK4182136 was demonstrated to induce ADCP by CD14+ monocytes.

In vivo

GSK4182136 was assessed for antiviral activity and the ability to decrease disease burden in SARS-CoV-2 infected Syrian Golden Hamsters (PC-7831-0119). A non-LS version of GSK4182136, VIR-7831-WT, was used as a surrogate for *in vivo* testing and since human IgG1 does not activate hamster Fc gamma receptors, this model solely evaluates the effects of neutralisation on disease.

Two different paradigms were tested. In the first VIR-7831-WT was administered via ip injection at Day-1 at doses of 0.05, 0.5, 5 or 30 mg/kg prior to inoculation with SARS-CoV-2. Based on the PK profile this paradigm was suggested to be reflective of IV antibody administration with Tmax reached at 24-36 h post dosing. In the second setting VIR-7831-WT was administered via ip injection at Day-2 at doses of 0.05, 0.5, 5 or 15 mg/kg) prior to inoculation with SARS-CoV-2, which was considered more reflective of a prophylactic treatment. In this hamster model weight loss was utilised as a surrogate for clinical disease. In the hamsters' dose at Day -1 a statistically significant decrease in weight loss was seen at the 5 and 30 mg/kg dose groups compared to vehicle. This correlated with statistically significant decreases in total viral RNA, or infectious virus levels based on $TCID_{50}$ measurements, in the lungs at both 5 and 30 mg/kg dose levels. Similarly, in the Day-2 groups statistically significant decreases in weight loss and total and infectious viral RNA load in the lung were seen for the 5 and 15 mg/kg dose groups. In the lower dose groups in which no effects were seen on the measured parameters (0.05 and 0.5 mg/kg) there was no evidence of enhancement of disease based on weight loss or viral loads suggesting some evidence for a lack of ADE in this model.

Secondary Pharmacology

Assessment of antibody-mediated enhancement (ADE).

The effect of GSK4182136 on the various potential mechanisms of ADE was explored *in vitro*. Enhancement of viral internalisation and replication of SARS-CoV-2 was evaluated in human cells that express FcγRs: monocyte-derived dendritic cells (moDCs), peripheral blood mononuclear cells (PBMCs) and U937 macrophage cells, allowing assessment of Fc-dependent mechanisms of ADE of infection. The effect of low concentrations of antibody on enhancement of infection in permissive Vero E6 cells (that do not express FcγRs) was also explored to evaluate ADE by enhanced kinetics of viral fusion in vitro. In addition, the potential for enhancement of Fc-mediated cytokine and chemokine production in the presence of GSK4182136 in the context of SARS-CoV-2 infection was evaluated.

GSK4182136 was evaluated at ~1X EC_{50}, as well as at subtherapeutic concentrations down to ~0.001X EC_{50}. No entry of SARS-CoV-2 into moDCs, PBMCs, or U937 cells was observed, while VeroE6 control cells demonstrated internalisation. No enhancement of viral internalisation in any cell type evaluated at any concentration tested compared to both the negative control antibody as well as the no antibody wells, with reduced internalisation of SARS-CoV-2 in VeroE6 cells was observed at the highest concentration of GSK4182136. No replication of SARS-CoV-2 was detected in moDCs, PBMCs or U937 cells regardless of GSK4182136 treatment, indicating lack of productive SARS-CoV-2 infection of these cells. Replication in the control VeroE6 cells was detectable at all antibody concentrations evaluated.

To evaluate the potential for VIR-7831 to enhance cytokine release upon SARS-CoV-2 infection in FcγR-expressing cells, cytokines and chemokines were measured in the supernatants from cells infected with SARS-CoV-2-in the presence of VIR-7831. Levels of IFN-γ, IL-10, IL-6, IL-8, IP-10, MCP-1, and TNF-α in the supernatant were quantified by MSD at 24- or 48-hours post-infection. For all cell types evaluated, cytokine/chemokine production was similar between the highest antibody concentration tested and the no antibody control at both 24 and 48-hours post-infection.

Safety Pharmacology

No *in vitro* assessment for the potential for delayed ventricular repolarisation has been performed as appropriate for a monoclonal antibody. In line with the guidance in ICH S6 (R1), no standalone safety pharmacology studies have been performed. In the 2-week repeat-dose IV infusion GLP toxicology study in cynomolgus monkeys (TX-7831-0102). ECGs, blood pressure and heart rate were monitored pre-study and on Day 8 at 2 hours post receiving the 2nd dose. Neurological exams were evaluated at pre-study, on Day 2 after the 1st dose; and respiratory function was evaluated at prestudy, on Day 8 after the 2nd dose at 4 hours after completion of infusion. No test article-related changes in safety pharmacology endpoints were seen at up to 500 mg/kg/dose of GSK4182136.

Pharmacodynamic Drug Interactions

To demonstrate that GSK4182136 does not interfere with other COVID-19 treatments, *in vitro* studies were conducted with GSK4182136 in combination with the antiviral, remdesivir, or another monoclonal antibody targeting a different epitope on the spike of SARS-CoV-2, bamlanivimab. In these studies, no antagonism was observed and the combination of GSK4182136 resulted in additive effects.

In summary, the provided nonclinical pharmacology studies provide evidence of the ability of GSK4182136 to bind the SARS-CoV-2 spike protein and neutralise its activity *in vitro*. The epitope to which GSK4182136 binds has been identified and appears highly conserved based on available sequences.

In vitro binding assays showed that VIR-7831 binds to a highly conserved spike epitope on SARS-CoV-2 spike RBD. VIR-7831 demonstrates high affinity binding to the SARS-CoV-2 spike RBD. VIR-7831 neutralizes SARS-CoV-2 virus in vitro with an EC50 of 100.1 ng/mL and effectively neutralizes pseudotyped virus containing the SARS-CoV-2 spike. VIR-7831 retained effectiveness against the UK B.1.1.7, South Africa B.1.351, Brazil P.1 and California CAL.20C variants in the VSV/VeroE6 pseudotyped virus system, with average fold change in EC50 values compared to relative Wild type sequence (YP_009724390.1) of up to 2.3.

In vitro selection experiments suggested a high barrier to resistance. Amino acid substitutions identified in resistance selection studies and subsequent pseudotyped virus neutralisation assays suggested that the E340A variant as a monoclonal antibody resistance mutant with an increase in EC_{50} of greater than 100-fold. This variant has not been detected in circulating strains although an E340K variant has, and for which no binding or neutralisation data is available. Since E340 is part of the epitope to which GSK4182136 binds, it is likely to be of clinical relevance.

VIR-7831 binds FcγRs in a manner consistent with human IgG1 and demonstrates the potential for ADCC and ADCP based on in vitro studies. In combination studies with remdesivir or bamlanivimab, VIR-7831 showed additivity with each agent and no antagonism was observed in either study.

VIR-7831 was also examined for the potential for ADE using a series of in vitro studies. Using moDCs, PBMCs, and U937 cells VIR-7831 showed no enhancement of viral uptake, no enhancement of viral replication, and no effect on infection-associated cytokine production. In an in vivo Syrian hamster model of VIR-7831 did not show any sign of potential for ADE either, but showed a dose-dependent improvement in body weight loss, viral load in hamster lung tissue, infectious virus load per gram of lung tissue in hamsters dosed with VIR-7831 on Day -1 or Day -2 before inoculation with SARS-CoV-2. However, no histopathology of the lungs appears to have been performed. Furthermore, no evidence was seen for ADE at sub-neutralising doses in this study.

Taken together the provided pharmacology studies support the proposed conditions of use. These conclusions are made based on the summaries provided as the study reports, which underpin the claims provided in the summaries, have not been assessed. This will be further assessed within the appropriate framework.

Pharmacokinetics

Absorption

In a single dose study GSK4182136 was administered intravenously to cynomolgus monkeys at a dose of 5 mg/kg and blood samples collected over a 56-day period to analyse for GSK4182136 levels and ADAs. No marked sex differences in PK parameters were observed and a half-life of 17.7 days was calculated. All animals were negative for ADA through day 56.

Pharmacokinetics were also measured as part of the repeat dose toxicity study in cynomolgus monkeys following intravenous administration of vehicle or GSK4182136 at 50 mg/kg, 150 mg/kg, or 500 mg/kg once weekly for 2 doses with blood sampling for up to 105 days post last dose. Serum levels were measured using a validated ELISA method (quantitative range was 50 to 5000 ng/mL). Both C_{max} and AUC values increased in a dose proportional and independent of sex. The accumulation ratio after the second dose were less than 2 at all dose levels suggesting no marked accumulation. Twelve out of 40 animals were ADA positive and ADA was detected across all dose groups with the highest incidence in the 150 mg/kg dose group, peaking at Day 29.

Distribution

Following a single IV administration of VIR-7831 at 5 mg/kg in cynomolgus monkeys (n=6; PK-7831-0115), the volume of distribution was 89.6 mL/kg, indicating limited distribution outside the vascular space, which is consistent with other IgGs. A study is ongoing to determine the levels of GSK4182136 in tissues, including lung and other tissues of the respiratory tract, relative to blood following a single IV administration of ^{89}Zr-labelled GSK4182136 to female monkeys (n = 3) on Day 0 and PET/CT imaging on Days 1, 3, 6, 10 and 14.

Metabolism and excretion

No studies have been conducted. This is acceptable, and in line with ICH S6(R1). GSK4182136 is expected to be metabolised into its constituent amino acids in a similar manner to endogenous IgG.

Pharmacokinetic Drug Interactions

No nonclinical PK drug interaction studies have been conducted with GSK4182136. This is acceptable for a monoclonal antibody directed against a foreign host protein.

In summary, the limited nonclinical pharmacokinetic studies submitted are considered sufficient.

Toxicology

A limited package of toxicological studies has been performed for GSK4182136 in-line with the requirements as outlined in ICH S6 (R1) for a monoclonal antibody targeting an exogenous viral target and for which there is no pharmacologically relevant species. Whilst the studies were performed in a non OECD-MAD country, the facility in which they were conducted has been subject to inspections by an EU GLP monitoring authority which has issued certificates of compliance for conducting nonclinical safety studies in line with the OECD principles of GLP.

Single dose toxicity

No stand-alone single dose studies have been performed which is acceptable.

Repeat dose toxicity

A 2-week repeat-dose intravenous infusion toxicology study with TK and 105-day recovery in cynomolgus monkeys and a single dose intramuscular injection site reaction study in minipigs were conducted to characterise GSK4182136. In addition, tissue cross-reactivity studies in normal monkey and human tissues and a non-GLP cross-reactive binding assay using a protein array enriched for human embryofetal proteins were conducted. Apart from the last study described above, the remaining studies claimed GLP compliance.

No toxicity and no infusion reactions with VIR-7381 were identified in the cynomolgus monkey 2-week repeat-dose IV infusion toxicology study up to 500 mg/kg (infusion rate 250 mg/kg/hr), the no-observed-adverse-effect-level (NOAEL) and highest dose tested.

Anti-drug antibodies were detected in some monkeys but had no effect on TK or impact on interpretation of toxicology. At the NOAEL of 500 mg/kg, Cmax and total exposure AUC (AUC from time 0 to end of recovery) were 13500 µg/mL and 216000 day•µg/mL, respectively, sexes combined. No injection site reactions were noted following a single intramuscular injection of 250 mg VIR-7381 (4 mL at 62.5 mg/mL) to minipigs.

Genotoxicity

No studies have been performed and as per ICH S6 (R1) it is not expected that monoclonal antibodies would interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies for GSK4182136 are planned because it binds to an exogenous or foreign target (per ICH S6(R1)).

Reproductive and Developmental Toxicity

Nonclinical reproductive and developmental toxicity studies will not be conducted for GSK4182136 because it binds to an exogenous or foreign target (per ICH S6(R1)).

Reproductive tissues from both sexes were evaluated as part of the 2-week toxicity study (all males were sexually mature except one high dose male was peripubertal). At the NOAEL, exposure in monkey (total AUC) was 61X estimated exposures (AUCinf predicted prior to FTIH) for the proposed 500 mg human dose. The data from nonclinical studies support the safety of VIR-7381 for treatment of COVID-19 in accordance with the proposed dose route and regimen.

Local tolerance

The local tolerance of GSK4182136 was assessed in the GLP 2-week repeat-dose toxicology study in cynomolgus monkeys which used the clinical route of administration, IV infusion, and did not show any evidence of treatment-related local injection site reactions at doses comparable or greater than those proposed for clinical evaluation.

In addition, a single dose intramuscular injection site reaction study in minipigs was conducted to evaluate the local injection site irritation potential of GSK4182136. The study was conducted using female animals who each received 250 mg. There were no test article-related clinical observations, no local injection site irritation or effects on body weight or food consumption. There were no test article-related macroscopic or microscopic findings.

Tissue cross-reactivity

The tissue cross-reactivity studies in normal cynomolgus monkey and human tissues and the human foetal protein cross-reactivity study did not identify off-target binding with VIR-7381 at 1 and 5 µg/mL. Appropriate positive and negative controls as well as tissue controls were included in the study. VIR-7831 did not bind to any of the normal cynomolgus tissues tested in this study.

Exposure margins

In the GLP repeat-dose toxicity study, at the NOAEL of 500 mg/kg, Cmax and total exposure AUC (the sum of AUC0-t after Day 1 and AUC0-last after Day 8) were 13500 µg/mL and 216000 day•µg/mL, respectively. Using a direct mg/kg conversion according to FDA guidance on proteins administered intravascularly with Mr > 100,000 daltons; (FDA 2005) 500 mg/kg in equivalent to a 30,000 mg fixed dose (using human body weight of 60 kg). Using a safety factor of 10, the maximum recommended starting dose in humans is approximately 50 mg/kg or 3000 mg fixed dose. Based on the 500 mg human dose, the margins based on the Dose, predicted human Cmax, and predicted AUC (total exposure AUC from TX-7831-0102 and expected AUCinf in humans) are 60-, 87-, and 61-fold, respectively, supporting the proposed clinical dose of 500 mg. See table below:

Table 40 – Dose and exposure margins based on NOAEL of 500mg/kg observed in the repeat-dose toxicity study

Proposed human dose (mg)	NHP NOAEL[a] (mg/kg)	Dose-based[b]			C_{max}-based			AUC-based		
		Dose (mg/kg)	Dose (mg)	Dose Margin	Monkey C_{max} Dose 2 (µg/mL)[c]	Human C_{max} (µg/mL)[d]	Exposure Margin	Monkey Total Exposure AUC (day•µg/mL)[e]	Human AUC_{inf}, (day•µg/mL)[d]	Exposure Margin
500	500	500	30000	60	13500	155	87	216000	3550	61

[a] NOAEL based on GLP repeat-dose toxicity Study TX-7831-0102
[b] Dose (mg/kg) was determinedvia direct mg/kg conversion according to FDA guidance on proteins administered intravascularly with Mr > 100,000 daltons (FDA 2005), assuming human body weight of 60 kg
[c] Monkey C_{max} after second IV dose at NOAEL
[d] Human C_{max} and AUC_{inf} are predicted values from simulated PK profiles for a single 500 mg IV dose
[e] Total exposure AUC = AUC_{0-t} after Day 1 + $AUC_{0\text{-last}}$ after Day 8, sum based on raw data

Discussion

Whilst the completed nonclinical toxicity studies are limited, they are in-line with the expectations as outlined in the relevant guideline, ICH S6 (R1), for a monoclonal antibody directed against a foreign host protein.

In the repeat dose toxicity study in cynomolgus monkeys (i.v. administration) no adverse effects were identified, and the high dose group of 500 mg/kg was selected as the NOAEL. Reproductive tissues were examined, and no changes were identified This NOAEL gives rise to exposure margins of at least 60-fold, based on human PK modelling. The exposure margins should be based on actual human PK data when available.

A local tolerance study in minipigs were performed using the i.m. route of administration. The dose of 250 mg VIR-7831 was well tolerated at a dose volume of 4 ml administered in the left lateral neck. Saline of a similar volume served as control on the right side. The study description does not offer any information as to the weight of the animals, however, a body weight of at least 8 to 16 kg would allow for an administration volume of 4 ml, if you administer maximum or the recommended dose of 0.5 or 0.25 ml/kg per injection site (Diehl et al 2001[4]). However, as no injection site reactions were noted at all, the dose volume was probably within acceptable limits.

No cross reactivity was observed in either monkey nor human tissue panels, at 1 and 5 µg/mL.

Most of the studies were conducted in China. The site has been inspected regularly by BE GLP inspection authority. FDA has also conducted inspections of the site. In addition, the studies supporting the current clinical development and future MAA, have been subject to inspection by an independent consultant on the Sponsors invitation. Although the use of such a consultant would not suffice to support the OECD GLP demands, it does offer a support for the validity of the data gathered.

Of note, these conclusions are made based on the summaries provided as the study reports, which underpin the claims provided in the summaries, have not been assessed. This will be further assessed within the appropriate framework.

2.4. Quality aspects

2.4.1. Introduction

Sotrovimab (GSK4182136, VIR-7831) is an engineered human immunoglobulin monoclonal antibody of the IgG1κ subtype.

VIR-7831 finished product is presented as a concentrate for solution for infusion and is supplied in vials. Each vial contains 500 mg of Sotrovimab as active substance in 8 mL (62.5 mg/mL). VIR-7831 is formulated with L-histidine and L-histidine monohydrochloride buffer, L-methionine buffer, sucrose, polysorbate 80 and water for injections. The formulation is sterile and does not contain any preservatives.

After dilution with sodium chloride 9 mg/mL (0.9%), the diluted solution of VIR-7831 must be administered intravenously immediately. If immediate administration is not possible, the diluted solution may be stored for up to 4 hours at room temperature (20°C to 25°C) or refrigerated up to 24 hours (2°C to 8°C).

2.4.2. Active Substance

General Information

Sotrovimab is an engineered human IgG1 monoclonal antibody that specifically binds to a highly conserved epitope on the spike protein receptor binding domain (RBD) of SARS-CoV-2. This in turn blocks viral cell-fusion, preventing SARS-CoV-2 invasion of human cells, and thus inhibits viral replication.

Sotrovimab consists of two identical light chains and two identical heavy chains. The theoretical molecular mass of intact VIR-7831 with the most common glycosylation pattern is 149 kDa when

[4] Diehl KH, Hull R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal JM, van de Vorstenbosch C; European Federation of Pharmaceutical Industries Association and European Centre for the Validation of Alternative Methods. A good practice guide to the administration of substances and removal of blood, including routes and volumes. J Appl Toxicol. 2001 Jan-Feb;21(1):15-23. doi: 10.1002/jat.727. PMID: 11180276.

expressed without heavy chain C-terminal lysine. The amino acid sequences of the heavy and the light chain have been provided.

Sotrovimab binds to the SARS-CoV-2 RBD and shows potent neutralisation of live virus *in vitro*. In addition, Sotrovimab is able to engage in Fc-mediated receptor activities, providing an additional potential mechanism for viral clearance.

The biological and physico-chemical properties of Sotrovimab have been sufficiently described.

Manufacture, process controls and characterisation

Manufacture

Information regarding the manufacturing and testing sites and their EU GMP status was provided.

VIR-7831 is produced using a suspension-adapted Chinese Hamster Ovary (CHO) cell line. The manufacturing process is considered standard for the production of monoclonal antibodies and has been sufficiently described consisting of an upstream (cell culture and harvest) and downstream purification processes. Purification is performed with a series of chromatography steps, ultra-/diafiltration steps and viral inactivation and filtration steps. The active substance is blast frozen, stored at the active substance manufacturing site and transported on dry ice under controlled temperature conditions for finished product manufacture.

Control of materials

Raw materials used in manufacture of VIR-7831 are described. Overviews of the raw materials used in the establishment of the cell bank, upstream raw materials and downstream raw materials including chemical grade or pharmacopoeial standard where relevant have been provided. Information about the resins, membranes and depth filters used in the active substance manufacturing process operations are also described.

Overall, the information provided on the raw materials used can be considered acceptable in the context of this procedure.

Control of critical steps and intermediates

Process parameters for the upstream unit operations are registered and are considered appropriate to control the upstream process. The control strategy for the downstream purification process is adequate. Process parameter target ranges are described and acceptance criteria or action limits are defined for the quality attributes tested at each unit operation.

Overall, the specified critical process parameters (CPPs) and quality attributes, in-process controls (IPCs), and associated preliminary acceptance criteria or action limits, are found acceptable.

Process validation

No formal validation of the active substance manufacturing process has been performed at this stage of product development, which is acceptable in the context of this procedure. Formal process validation studies will be expected at the time of marketing authorisation application (MAA).

Manufacturing process development

Information to support the various process changes introduced during the active substance manufacturing process development has been provided. An extensive comparability exercise including comparison of the stability of material from the different processes will be expected at the time of MAA in accordance with ICH Q5E.

Characterisation

A comprehensive characterisation was performed to elucidate the structure and other characteristics of Sotrovimab using state-of-the art methods, with emphasis on primary structure, size and charge heterogeneity, extinction coefficient, glycans, and biological activity. Post-translational modifications were also examined. Details on the biological activity have been determined using separate orthogonal analytical methods.

An overview of process- and product-related impurities has been provided. Overall the information provided is acceptable for this stage of development and in the context of this procedure.

Specification

Specifications and acceptance criteria are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. The justification provided for the specifications is acceptable in the context of this procedure. It is noted that the test panel and acceptance criteria will be revised at the time of MAA as additional experience is gained with the manufacturing process and additional analytical data are obtained.

Analytical procedures

The broad panel of analytical methods used for release and stability testing of VIR-7831 active substance is generally considered relevant for the control of a monoclonal antibody. For pharmacopoeial tests reference is made to the relevant Ph. Eur. monographs. All non-compendial analytical procedures used to test VIR-7831 have been validated for both active substance and finished product where relevant and are suitable for their intended purpose.

The information provided for this stage of development and in the context of this application is overall considered acceptable.

Batch analyses

Representative batch analyses data has been provided for the manufacturing process of Sotrovimab. They are all well within the current active substance release specification acceptance criteria.

Reference standard

A reference standard (RS) has been developed for use in qualitative, quantitative and semi-quantitative testing of in-process samples, active substance and finished product to verify consistent product quality and assay performance. Results of release testing demonstrate that the reference standard is comparable and comply with all active substance release acceptance criteria. Additional characterisation tests have also been performed.

For the qualification of future RS, the current reference material will be used as the standard for comparison against the proposed RS to ensure lot-to-lot consistency. All reference standards are re-evaluated annually for stability.

Container closure

The container closure system for Sotrovimab active substance has been described.

Stability

Stability studies have been initiated using Sotrovimab active substance to evaluate its stability profile, and to assign a shelf life. The proposed shelf life at the recommended storage conditions is considered

acceptable in the context of this procedure and in line with the Guideline on biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1).

The Company will continue to evaluate the stability data in accordance with approved stability protocols and any extension to the established shelf life period will be based on the assessment of future stability data against the current established specification according to the relevant guidelines. Additional stability data will be expected at the time of MAA.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

VIR-7831 finished product is provided as a sterile, preservative-free concentrate for solution for infusion containing no novel excipients or excipients of human or animal origin. The excipients (L-histidine and L-histidine monohydrochloride buffer, L-methionine buffer, sucrose, polysorbate 80 and water for injections) are of pharmacopoeial grade and well established for use in pharmaceutical products for infusion. Each vial of VIR-7831 contains 500 mg of Sotrovimab as active substance in 8 mL (62.5 mg/mL).

The qualitative and quantitative composition for VIR-7831 was provided and is considered adequate.

Pharmaceutical development

The information provided to support the formulation development and manufacturing process development is considered acceptable in the context of this procedure.

Overall sufficient compatibility data has been provided to support administration as per the instructions in the Conditions for Use.

Manufacture of the product and process controls

Manufacture

The finished product manufacturing and testing sites and their EU GMP status were provided.

The finished product manufacturing process represents a standard process for monoclonal antibodies (i.e. consisting of pooling of active substance lots, dilution with formulation buffer, filtering, filling, stoppering, and capping). The vials and stoppers are sterilised according to validated processes prior to use.

IPCs and associated action limits/acceptance criteria have been provided.

Process validation

No formal validation of the finished product manufacturing process has been performed at this stage of product development, which is acceptable in the context of this procedure. Formal process validation studies will be expected at the time of marketing authorisation application (MAA).

Product specification

Specifications and acceptance criteria are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. The justification provided is acceptable in the context of this procedure. It is noted that the test panel and acceptance criteria will be revised at the time of MAA as additional experience is gained with the manufacturing process and additional analytical data are obtained.

Analytical procedures

Most analytical methods used to control the finished product are also used at the active substance level and thus are described and validated in the active substance section. Methods specific to the finished product have been sufficiently described.

Batch analysis

Batch analysis data for finished product batches have been provided. The results are all well within the current finished product release specification acceptance criteria.

Reference standard

The reference standard used for the finished product testing is the same as for the active substance.

Container closure

A description of the components of the container closure system used for the finished product has been provided.

The container closure system was selected due to its ability to maintain container closure integrity during storage of the injectable product at the recommended storage conditions and its general compatibility with biopharmaceutical products. The vial and the stopper are composed of typical materials used in the packaging of sterile pharmaceutical products.

Stability of the product

A shelf-life of 12 months is proposed for the finished product at the long-term storage condition at 2°C to 8°C.

The stability of the finished product is being monitored at three conditions: long-term, accelerated, and stressed. The observed changes in product quality at stressed conditions are typical for monoclonal antibodies. No meaningful changes were observed during the stability studies at long-term conditions.

Based on the stability data provided the proposed shelf life is acceptable and in line with the requirements for shelf life determination outlined in the Guideline for biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1).

At the time of MAA, shelf life determination should be based on ICH Q5C principles and additional stability data will be expected.

After dilution, the diluted solution of VIR-7831 must be administered intravenously immediately. If immediate administration is not possible, the diluted solution may be stored for up to 4 hours at room temperature (20°C to 25°C) or refrigerated up to 24 hours (2°C to 8°C).

Adventitious agents

No animal- or human-derived raw materials with a risk for virus or TSE contamination are used in the manufacture of VIR-7831. The cell line and the cell banks have been extensively tested and found to be free of adventitious agents.

The testing programme presented for non-viral agents is found sufficient.

An adequate programme is in place to ensure an acceptable viral safety profile for VIR-7831. The viral clearance results have been presented and the clearance levels are found sufficient to ensure acceptable viral safety.

In conclusion, the risk of contamination of VIR-7831 with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of viral contaminants in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity demonstrated for the VIR-7831 purification process.

2.4.4. Discussion

Overall, the quality of VIR-7831 is considered adequate and sufficiently demonstrated in view of the data provided by the Company on the manufacture, characterisation, pharmaceutical development, control and stability of the active substance and finished product, for this stage of development and in the context of this procedure.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of VIR-7831 is considered acceptable in the context of this procedure and the COVID-19 pandemic, when used in accordance with the Conditions for Use.

3. Overall conclusions

Despite the ongoing vaccination campaigns throughout the EU there is still a medical need for therapeutics for the treatment of COVID-19, especially in subjects who for various reasons are at high risk of severe COVID-19.

VIR-7831 is a highly specific mAb expected to retain activity against spike variants that confer reduced susceptibility to other mABs. Beside virus neutralisation activity, *in vitro* data showed indirect antiviral mechanisms, antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), which may also contribute to its clinical effectiveness.

Quality aspects

The overall quality of VIR-7831 is considered acceptable in the context of this procedure and the COVID-19 pandemic, when used in accordance with the Conditions for Use.

Non-clinical aspects

Proof of concept has been established in non-clinical studies. While most of the non-clinical studies have been conducted in China and therefore not EU or OECD GLP certified, regular inspections by both Belgian authorities and FDA support the validity of the data. VIR-7831 retained effectiveness against the UK B.1.1.7, South Africa B.1.351, Brazil P.1 and California CAL.20C variants, but a few mutations (E340A, E340K as well as P337R,D614G) were found to be monoclonal antibody resistant mutants, with a >100 fold change in EC50 compared to wild type SARS-CoV-2 virus. The nonclinical *in vitro* data using VIR-7381 and *in vivo* data using VIR-7381-WT and hamster chimeric S309 did not identify a potential for ADE. The toxicity study package is small but considered sufficient in the context of this procedure, as the product is a human mAb against a non-endogenous target and no cross reactivity was observed in either monkey or human tissue panels.

Clinical aspects

The pivotal study for this procedure is the COMET-ICE study: a randomised, double-blind, multi-centre, placebo-controlled efficacy/safety study to assess the use of VIR-7831 for the early treatment of COVID-19 in non-hospitalised patients who are at risk of disease progression. Risk factors included older adults (age ≥55 years) or specific comorbidities, including diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate-to-severe asthma. VIR-7831 treatment could be relevant for severely immunocompromised participants, but these were excluded from the study. Subjects previously vaccinated against COVID19 were also excluded.

The assessment of this study was performed based on an interim analysis with data cut off 04 March 2021. The study design was considered appropriate. The plans for the interim analyses were found broadly acceptable. It was considered essential that analyses for futility were planned due to lack of any data that could predict efficacy. However, it would have been preferred that the Lead-in phase patients were excluded from the primary analysis of efficacy since they could not be adequately assessed for the primary endpoint.

The revised primary endpoint that required only hospitalisation >24 hours or death is considered suboptimal. This is due not only because of different thresholds for hospital admission and discharge in different healthcare systems but also because some patients are hospitalised simply because they cannot be cared for at home for some reason or as a precaution because of other conditions. Due to these concerns regarding the lack of sensitivity of the final primary endpoint to detect a true effect of the intervention on the course of COVID-19, it is essential to highlight the effects on the secondary endpoints, several of which capture changes in clinical condition rather than placement of the patient.

Based on the ITT population of 583 patients, there were very few dropouts in this single dose study. It is unfortunate that not all had RT-PCR confirmation of SARS-CoV-2. Nevertheless, in the context of a pandemic, it is expected that the antigen detection test results were likely accurate in all or most cases. Nasal samples have been sequenced from 126 subjects. Of the 104 baseline samples none carried the SARS-CoV-2 UK (B.1.1.7), South Africa (B.1.351) or Brazil (P.1) variants. Hence, the available data from COMET-ICE are insufficient to support any claims about efficacy of VIR-7831 against variants. Based on *in-vitro* susceptibility data and given that VIR-7831 is given once to patients with mild disease at baseline, the serum concentrations are projected to be sufficient to exert an antiviral effect against the majority of currently circulating variants until recovery from the acute illness. At present, variants with the E340K mutation are unlikely to be treatable.

The study population included 22% of patients aged 65 years and over and 11% aged 70 years and over. The majority was overweight or obese. Very few had CHF or renal disease, and none was immunosuppressed. Despite this, the applicant proposed that sotrovimab is for use specifically in patients with a very long list of possible risk factors, including some that were not present in the study population. There is a lack of evidence regarding the contribution of several of the listed risk factors linked to development of severe COVID. In stratified analysis it is clear that some of the risk factors (asthma and BMI>30) did not increase the risk for hospitalisation, whereas older age and diabetes were associated with a higher risk of hospitalisation in subjects with COVID-19.

As such, the study population was not fully representative of the proposed target. However, the conclusion of a reasonable likelihood of benefit may be extrapolated to such patients and the target population for use of sotrovimab, is considered acceptable in the context of this Article 5(3) procedure.

The planned IA1 met the criteria for success. VIR-7831 resulted in a statistically significant reduction in the proportion who required >24 hours of hospitalisation for acute management of any illness or died from any cause through Day 29. The reduction was by 85% (adjusted relative risk reduction)

(p=0.002). However, this 85% reduction translates into a very modest effect since the actual rates were 7% in the placebo group and 1% in the VIR-7831 group. It is important to note that there was only one death recorded up to Day 29 (in the placebo group), which means that the primary analysis is driven by a reduction in the need for a hospital stay of at least 24 hours. Three (<1%) patients in the placebo arm where administered concomitant remdesivir (apparently when they progressed) but no patient in the VIR-7831 arm. Therefore, the effect of VIR-7831 has been estimated in the absence of remdesivir.

Most importantly, VIR-7831 resulted in numerical reductions in the need for supplementary oxygen and progression to severe and/or critical respiratory COVID-19. No patient treated with VIR-7831 required high flow oxygen, oxygen via a non-rebreather mask or mechanical ventilation through Day 29 compared to 7 in the placebo group. Moreover, 11 placebo vs. 2 VIR-7831 patients required oxygen by mask or nasal cannulae. These results and the reasons given for hospitalisation support a conclusion that VIR-7831 has some benefit on the risk of progression, even though this was not the final primary endpoint of the study.

Although 58% were enrolled when they had ≤3 days of symptoms and 42% when they had 4-5 days of symptoms, the comparisons made between the two pre-planned strata must be viewed with caution because of the paucity of events. Nevertheless, it does not seem relevant how long symptoms had been present at least up to 5 days, after which there are no data. In this mildly ill target population, a monoclonal antibody directed at the virus is less likely to have a significant effect on outcomes as time from onset increases.

The infusion time in COMET-ICE was 60 minutes while the applicant proposes 30 minutes in the conditions for use. This proposal is based on safety data from BLAZE-4 in which 30-minute infusion times are used and the observation that peak serum concentrations for monoclonal antibodies are independent of the infusion time. This proposal is acceptable.

In COMET-ICE, safety data are reported for 868 patients with a median duration of follow-up of 56 days (range 5-190). Of the 868, 747 were followed through >29 days and 18 of these had been followed for 24 weeks. Unsolicited adverse events were collected by communication with the participant, whereas solicited adverse events were collected in diaries. Instruments for patient reported outcome measures (Flu-PRO Plus) or quality of life were not used to capture adverse events.

At present, results from FLU-Pro plus and the questionnaires are not reported, which is not critical for this Article 5(3) procedure.

Generally, the safety data do not point to any major concerns for use of VIR-7831 in the target population. Infusion-related reactions can occur with humanised monoclonal antibodies, some of which may be severe so that vigilance is needed during and for a while after the infusion. Anaphylaxis has been reported with VIR-7831, which is not unexpected. Patients were observed for 2 hours after completion of infusion. As there has not been identified any increase in risk of infusion related reactions or anaphylaxis compared to other monoclonal antibodies monitoring for 1 hour after infusion is considered adequate.

Of the AEs reported in ≥1% of patients, diarrhoea was reported more frequently with VIR-7831 (6 [1%] vs. 3 [<1%] placebo). It does not appear that other AEs occurred more often with VIR-7831 than with placebo. The applicant has listed the 7 most common AEs in the Conditions for Use rather than ADRs. According to the data provided, 8 patients (2%) in each treatment group had an AE considered related to treatment, none of which in the VIR-7831 group was a SAE. One AE in the VIR-7831 group and 2 in the placebo group were treatment-related infusion reactions. However, no tabulation of ADRs have been provided. As the number is considered low, and as none of the drug

related events are severe, it is considered acceptable that the Applicant does not present a list of ADR for this procedure. Further details on ADRs should be provided within the appropriate framework.

The overall frequency of AEs was higher in participants older than 65 years, however, the frequency was higher in the placebo group compared with VIR-7831 for both AE and SAE. For the 1% most frequent adverse events in participants older than 65 years, COVID-19 pneumonia occurred in 4% (3 participants) in VIR-treated participants and in 3% (3 participants) in the placebo arm. As VIR-7831 is expected to have an effect on COVID-19 pneumonia, it is a bit surprising that no difference in COVID-19 pneumonia is observed among participants older than 65 years. This is not pursued further for this article 5(3) procedure but should be further addressed within the appropriate framework.

No immunogenicity data are available at present. However, VIR-7831 is intended to be given only once. Efficacy and safety in subjects previously vaccinated against COVID-19 is not available at present either. The lack of data is reflected in the Conditions for Use.

Additional preliminary safety information has been provided from ACTIVE-3-TICO, which is useful especially with regard to documenting IRRs. The safety database is rather limited but considered to be sufficient for the purposes of this Article 5(3) procedure.

The Committee considered that this medicine, once it is authorised for use, should be subject to additional monitoring. This enables to stimulate the ADR reporting in order for new safety information to be identified quickly. Healthcare Professionals will be asked to report any suspected adverse reactions.

A single dose of 500 mg was selected based on *in vitro* neutralisation data, *in vitro* resistance data, expected human PK extrapolated from a study in cynomolgus monkeys, and the results of the monkey toxicology study. Exposure is expected to be achieve supratherapeutic levels in plasma and pulmonary tissues and therapeutic levels in nasal tissues sufficient to prevent progression of COVID-19. Safety margins to NOAEL are reassuring. It could be of interest to further explore the effect of a lower dose in order to increase the availability of the product. However, VIR-7831 appears to be well-tolerated and the proposed single dose of 500 mg iv is considered acceptable. Extrapolation to adolescents from 12 years of age and with a body weight of at least 40 kg is acceptable.

Overall, monotherapy with VIR-7831 provided a relevant clinical benefit by reducing the risk of hospitalisation or death in the target population of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. The results of secondary endpoints, including several more relevant to patient clinical status, give support to a conclusion that VIR-7831 does have some benefit in patients who do not require oxygen supplementation.

Overall conclusion

Considering the data provided by the company on quality aspects, preclinical aspects and the provided clinical dataset, sotrovimab might provide clinical benefit for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19 in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions of use.