Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Xevudy 500 mg concentrate for solution for infusion

Sotrovimab

PLGB 19494/0301

The Public Assessment Report summarises the initial assessment at the time of approval in December 2021. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics.

GlaxoSmithKline UK Limited

LAY SUMMARY

Xevudy 500 mg concentrate for solution for infusion
sotrovimab

This is a summary of the Public Assessment Report (PAR) for Xevudy 500 mg concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Xevudy in this lay summary for ease of reading.

For practical information about using Xevudy, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Xevudy and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Xevudy is used in the treatment of symptomatic acute COVID-19 infection in adults and adolescents (from 12 years and weighing at least 40 kg).

How does Xevudy work?
Xevudy contains the active substance sotrovimab. Sotrovimab is a monoclonal antibody, a type of protein designed to recognise a specific target on the SARS-CoV-2 virus. Sotrovimab attaches to the spike protein of SARS-CoV-2 (the virus that causes COVID-19) thereby preventing the virus from entering the body's cells.

Xevudy is used to treat symptomatic acute COVID-19 infection in adults and adolescents (from 12 years and weighing at least 40 kg). It targets the spike protein that the virus uses to attach to cells. Xevudy can help your body overcome the infection and prevent you from getting seriously ill.

How is Xevudy used?
The pharmaceutical form of this medicine is a concentrate for solution and the route of administration is intravenous infusion. The recommended dose is a single 500 mg intravenous infusion administered following dilution.

For further information on how Xevudy is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Xevudy have been shown in studies?
Xevudy has been studied in non-hospitalised adult patients who did not require any form of oxygen supplementation at study entry. In this study 1,057 patients with COVID-19, and at

least one underlying condition that put them at risk of severe COVID-19, were treated with Xevudy or placebo. Results showed that Xevudy led to fewer patients requiring hospitalisation or dying within 29 days of treatment when compared with placebo. Of the patients at increased risk of their illness becoming severe, 1% of those treated with Xevudy (6 out 528) were hospitalised for longer than 24 hours within 29 days of treatment compared with 6% of patients on placebo (30 out of 529), 2 of whom died.

What are the possible side effects of Xevudy?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcardor search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Xevudy (which may affect more than 1 in 10 people) are hypersensitivity) reactions including skin rash and itching.

Why was Xevudy approved?
It was concluded that Xevudy has been shown to be effective in the treatment of symptomatic acute COVID-19 infection in adults and adolescents (from 12 years and weighing at least 40 kg). Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Xevudy has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Xevudy?
A Risk Management Plan (RMP) has been developed to ensure that Xevudy is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Xevudy
A Marketing Authorisation for Xevudy was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 1st December 2021.

The full PAR for Xevudy follows this summary.

This summary was last updated in October 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Xevudy 500 mg concentrate for solution for infusion (PLGB 19494/0301) could be approved.

The product is approved for the following indication: for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection (see section 5.1).

The active substance is sotrovimab. Sotrovimab is a monoclonal antibody (IgG1, kappa) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Sotrovimab is a dual action, engineered human IgG1 mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2.

In the COMET-ICE clinical trial post-baseline variants were detected in (i) the sotrovimab epitope of the spike protein and (ii) the receptor-binding motif of the spike protein. Post-baseline epitope substitutions detected in more than 2 participants in the sotrovimab arm at a frequency of >15% included P337L/R and E340A/K/V. Substitutions E340A/V/K and P337L/R confer reduced susceptibility to sotrovimab in an in vitro pseudotyped VLP system. The clinical impact of these substitutions is not yet known. In the receptor-binding motif of the spike protein, the substitutions K417T, S477N, E484K, and N501Y were detected post-baseline in more than 2 participants in the sotrovimab arm at a frequency of >15%. Sotrovimab retains activity against K417T, S477N, E484K, and N501Y in an in vitro pseudotyped VLP system.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of the rolling review licensing route. The rolling review process is intended to streamline the development of novel medicines. As part of the process the applicant submitted increments of the dossier for pre-assessment by the MHRA, rather than submitting a consolidated full dossier at the end of the product development process.

This product has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Xevudy 500 mg concentrate for solution for infusion. The CMA for Xevudy 500 mg concentrate for solution for infusion, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) P/0468/2021.

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 17 November 2021 in relation to a post-licensing exercise to monitor the appearance of variants in those exposed to the current product.

A national marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 1 December 2021.

II QUALITY ASPECTS

II.1 Introduction

Each single-use vial of product consists of 500 mg of the active substance (sotrovimab) in 8 mL (62.5 mg/mL).

In addition to sotrovimab this product also contains the excipients histidine, histidine monohydrochloride, sucrose, polysorbate 80, methionine and water for injections.

The finished product is packaged in 10 mL Type I borosilicate clear glass single-use vials, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip-off cap.

II.2 ACTIVE SUBSTANCE

rINN: sotrovimab

Chemical Name: Immunoglobulin G1 [438-leucine, 444-serine], anti-(severe acute respiratory syndrome coronavirus 2 spike glycoprotein receptor-binding domain) (human monoclonal VIR-7831 γ1-chain), disulfide with human monoclonal VIR-7831 κ chain, dimer

Molecular Formula: C6480H10030N1738O2036S40

Chemical Structure:

Figure 1: Disulfide bond map

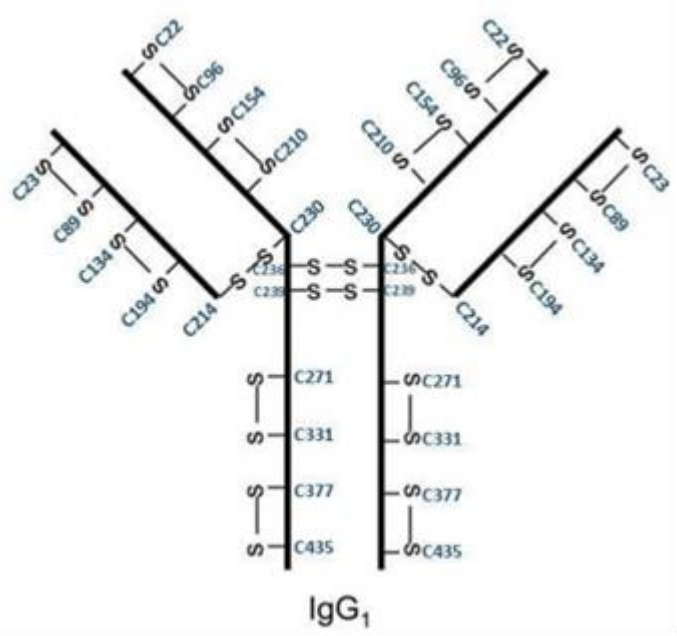

Figure 2: Amino acid sequence of sotrovimab

Heavy Chain Amino Acid Sequence

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  1 QVQLVQSGAE VKKPGASVKV SCKASGYPFT SYGISWVRQA PGQGLEWMGW
 51 ISTYQGNTNY AQKFQGRVTM TTDTSTTTGY MELRRLRSDD TAVYYCARDY
101 TRGAWFGESL IGGFDNWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA
151 ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS
201 SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV
251 FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK
301 PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
351 GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN
401 YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVLHE ALHSHYTQKS
451 LSLSPGK
```

The N-glycosylation site at Asn307 is shown as **N**.

Light Chain Amino Acid Sequence

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  1 EIVLTQSPGT LSLSPGERAT LSCRASQTVS STSLAWYQQK PGQAPRLLIY
 51 GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QHDTSLTFGG
101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC
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Molecular Weight: 146142 Da

Appearance: A clear, colourless or yellow to brown solution

Sotrovimab is not the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Manufacturing process
The manufacturing process intended for commercial production is overall standard for monoclonal antibodies using a suspension-adapted Chinese hamster ovary (CHO) cell line.

The drug substance formulation is sotrovimab in a L-histidine/L-histidine monohydrochloride buffer containing L-methionine, sucrose, and polysorbate 80 at a pH of approximately 6.0. Sotrovimab drug substance is stored and shipped frozen.

Control of materials
Overviews of the raw materials used in the sotrovimab DS upstream and downstream manufacturing process are provided, including their pharmacopoeial standards and corresponding usage in the process. The excipients used to formulate the DS and DP are tested according to Ph. Eur.

Overviews of the resins, membranes, depth filters and storage flask and bags used in the DS manufacturing process operations are also sufficiently described.

With the exception of the HCl and NaOH used for pH adjustment, the raw materials of non-compendial grade are as a minimum controlled for endotoxin by the raw material specifications. The resins are controlled for bioburden. The controls are considered acceptable.

The cell culture media and nutrient feeds are confirmed to be free of animal proteins.

No animal or human derived raw or starting materials are used in the manufacture of sotrovimab. Synthesis of the active substance from the designated starting materials has been adequately described. The critical process parameters (CPPs) and critical performance attributes (CPAs) as well as their acceptance ranges have been outlined. No process intermediates have been defined, only in-process pools. This is acceptable.

Results from process performance qualification (PPQ) validation studies confirmed that the parameters investigated were properly validated and contributed to high purity and quality of sotrovimab active substance.

The manufacturing process development has been adequately described as have the changes introduced between different process versions.

The proposed process characterisation studies are satisfactory and the assigned critical quality attributes (CQAs) and non-CQAs are appropriate.

Appropriate characterisation data have been supplied for the active substance. All active substance molecular variants have been identified and characterised as product-related substances or product-related impurities.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. An appropriate reference standard has been provided.

Suitable testing has been applied to all packaging used. The container closure specification is acceptable.

Appropriate stability data have been generated supporting the proposed active substance shelf life.

II.3 DRUG PRODUCT

Pharmaceutical development

The finished product is a sterile liquid supplied in a single-use vial containing 500 mg (62.5 mg/mL) of sotrovimab as active substance. The formulation includes the excipients 20 mM L-histidine/ L-histidine monohydrochloride buffer, 7% sucrose (w/v), 0.04% polysorbate 80 (w/v), 5 mM L-methionine, and water for injection. A satisfactory account of the pharmaceutical development has been provided.

The chosen excipients are all established components of monoclonal antibody liquid formulations. All excipient used in sotrovimab final product comply with the relevant Ph Eur monographs.

Representative certificates of analysis have been provided for each excipient

No excipients of animal or human origin are used in the finished product.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided. Sufficient data has been provided to justify that comparability was achieved between early process and commercial process.

An appropriate description and justification for the choice of container closure has been provided. It confirms to Ph Eur and USP requirements and is of an expected composition and design for a product of this type. Suitability, compatibility and safety are addressed, including microbial assurance.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Overall, the process validation demonstrate that the process performs consistently, and the proposed commercial process is considered supported.

Finished product specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications at the time of testing. Good batch-to-batch consistency was observed between the commercial batches. The same reference standard is used for both drug substance and drug product.

Container closure system
The primary packaging for the sotrovimab finished product consists of a 10R type 1 borosilicate glass vial with a 20-mm fluoropolymer-coated rubber stopper sealed with an aluminium flip-off cap.

The glass vial and rubber stopper comply with the relevant monographs. Specifications and schematic drawings have been provided. Extractables study and transportation validation has been submitted and is found acceptable. The provided stability data supports the suitability of the container closure.

Impurities
No new product-or process-related impurities are introduced during finished product manufacturing and the materials used during the finished product manufacturing are considered suitable for use and are not likely to leach components into the finished product material.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 1 year for the unopened vial is acceptable. The diluted solution for infusion is intended to be used immediately. If after dilution, immediate administration is not possible, the diluted solution may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2°C to 8°C) for up to 24 hours from the time of dilution until the end of administration.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
Sotrovimab (also known as VIR-7831, GSK4182136 and WBP2275) is a human immunoglobulin G1 kappa (IgG1κ). The antibody VIR-7831-WT is the same as sotrovimab, except that it lacks the Fc modification present in sotrovimab; VIR-7832 is a modification of

sotrovimab which contains both the LS modification present in sotrovimab and has an additional modification in its Fc region, not present in sotrovimab, which may be immune-modulating; the parental antibody from which sotrovimab was derived is termed S309: and GH-S309 is a hamster-human chimeric version of the parental antibody that has hamster Fc regions and human variable regions intended to interact with hamster FcR receptors.

Primary pharmacodynamics

In vitro primary pharmacodynamic studies

Study 2020n456937

In study 2020N456937, the binding of sotrovimab to SARS CoV-2 receptor binding domain was studied by an enzyme-linked immunosorbent assay (ELISA) and by surface plasmon resonance. Binding to SARS-CoV-2 spike protein displayed on the surface of mammalian cells was also evaluated.

Sotrovimab bound to recombinant SARS CoV-2 receptor binding domain in a concentration-dependent manner with a mean EC50 value of 20.40 ng/ml calculated from ELISA data. An equilibrium constant (KD) of 0.21 nM was determined from surface plasmon resonance (SPR) to a recombinant RBD domain of the spike protein. Flow cytometry testing found that sotrovimab bound to surface expressed spike protein. It was concluded that sotrovimab binds to SARS-CoV2-RBD as measured by SPR and ELISA and binds to cell surface expressed full-length spike protein.

In vitro neutralisation of SARs-Cov-2

Study 2020n457420

This study determined the neutralisation activity of sotorovimab against SARS-CoV-2 *in vitro*. Sotrovimab (VIR-7831) prevented entry of SARS CoV-2 virus into Vero E6 cells. Concentration dependent viral neutralisation was observed, with an average EC50 value of 100.1 ng/mL and EC90 of 186.3 ng/ml (range: 125.8 – 329.5 ng/ml) against the SARS-CoV-2 isolate USAWA1/2020 in VeroE6 cells.

Study 2021N475485

In study 2021n475485, the *in vitro* neutralisation activity of VIR-7831 against SARS-CoV-2 live virus variants from the UK (B.1.1.7), South Africa (B.1.351) and Brazil (P.1) was determined. Sotrovimab neutralised each of the South African, Brazil and UK variants with changes to the EC50 values of 1.2-, 1.6- and 3.0 -fold versus wild type virus, respectively.

In vitro neutralisation of SARs-Cov-2 pseudotyped virus

Study 2020n456924

The capacity of sotrovimab to neutralise SARS CoV-2 was tested using a vesicular stomatitis virus (VSV)-based pseudotyped virus system.

In this assay, a VSV-based luciferase reporter pseudotyped virus system with SARS-CoV-2 spike protein was used. Dose-dependent viral neutralisation by sotrivimab (VIR-7831) was observed with an EC50 value of 24.06 ng/ml (range: 20.56 – 28.60 ng/ml) and EC90 value of 107.72 ng/ml (range: 83.37 – 144.7 ng/ml).

Sotrovimab neutralization of circulating spike protein variants in SARs-CoV-2 pseudotyped virus

Study 2020N456987

Spike coding sequences deposited in the GISAID database from currently circulating SRS-CoV-2 were analysed for conservation of amino acids. The neutralisation activity of

sotrovimab against the most prevalent amino acid variants identified in the spike protein of circulating strains was evaluated in the SARS-CoV-2 pseudotyped virus as measured by concentration response (EC50 values). Sotrovimab neutralised all variants evaluated: EC50s ranged from 27.60-57.74 μg/ml, within < 2-fold change in EC50 relative to wild type (wild type EC50: 34.33 μg/ml).

Study 2021N470273
A luciferase reporter VSV pseudotyped virus system was used to determine if sotrovimab retains activity against 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.

The fold changes in EC50 values (concentration) of sotrovimab compared to wild-type to neutralise SARS CoV-2 variants were <3-fold for 18 out of 19 variants tested with the 19th showing 3.38-fold shift in EC50. Sotrovimab retained activity against pseudotyped virus expressing the B.1.1.7, B.1.351, P.1 and CAL.20C spike variants. Fold-changes in EC50 ranged from 0.35- to 2.30-fold indicating that sotrovimab remains active against these spike variants in this test system.

Epitope mapping of sotrovimab, epitope conservation in SARs-CoV-2,
The epitope targeted by sotrovimab was mapped using crystallographic methods.

Analysis identified that the epitope comprises 23 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. Neutralising activity of sotrovimab against SARS-CoV-2 pseudotyped virus expressing spike protein epitope variants was examined in studies 2021n476139 and 2021n477635 which also analysed the then current sequence conservation of SARS-CoV-2 spike amino acids that comprise the sotrivimab epitope. 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 for all positions including 14/22 amino acid positions ≥99.99 conserved.

To evaluate whether the amino acid variants identified in the epitope in circulating strains confer reduced susceptibility to sotrovimab, amino acid substitutions were introduced into the SARS-CoV-2 spike coding sequence and assessed in a SARS-CoV-2 pseudotyped virus neutralisation assay. Sotrovimab effectively neutralized epitope variants at most amino acid positions tested as measured by concentration response (EC50 values) (Study 2021N476139).

Binding of sotrovimab to SARS-CoV-2 spike variants detected in the epitope
In study 2021n477635, sotrovimab neutralised epitope variants at most amino acid positions tested but a moderate shift in potency was seen for the K356T and P337H/T variants and significant EC50 shifts were seen for E340 and P337 indicating reduced susceptibility to sotrovimab. Variants E340 and P337 were considered monoclonal antibody resistance mutations.

In study 2021N481341 sotrovimab retained activity against epitope variants at most amino acid positions evaluated in this report with fold changes in EC50 ranging from 0.67 to 2.45. P337K resulted in greater shifts in EC50 (>304-fold change) indicating reduced susceptibility for this variant.

In vitro resistance barrier assessment in the presence of fixed and increasing concentrations of mAb

Study 2020N456627

In vitro resistance-associated characteristics were assessed in study 2020n456627. This study was performed with VIR-7832, which is a modification of sotrovimab termed XX2. Sotrovimab and VIR-7832 are identical except that VIR-7832 includes the enhanced effector function and immune modulating "XX2" modification in the Fc domain SARS-CoV-2 was subjected to 10 passages in the presence of VIR-7832 at fixed concentrations of ~10X, 20X, 50X or 100X EC50 in VeroE6 cells. No detectable virus was observed at any concentration of VIR-7832 through all 10 passages.

A second method was then employed where virus is initially passaged in sub-EC50 concentrations of antibody followed by subsequent passaging in increasing concentrations of mAb in an attempt to force the emergence of variants that may potentially reduce susceptibility to sotrovimab. The virus was initially passaged in sub-EC50 concentrations of antibody, followed by subsequent passaging in increasing concentrations of mAb for up to 8 passages. Viral passages where a shift in neutralization (>2-fold relative to wild type) was detected were subjected to RNA isolation and subsequent sequence analysis of the spike gene. This analysis identified amino acid substitutions E340A, R682W, and V1128F.

Binding of sotrovimab to cell surface-expressed SARS-CoV-2 protein variants

Binding studies were performed using flow cytometry to detect antibody binding to cell surface-expressed SARS-CoV-2 full length spike protein encoding variants. Sotrovimab 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.

Conservation of SARS-CoV-2 spike variants

To determine the conservation of the amino acid residues identified as variants during in vitro resistance selection, available SARS-CoV-2 spike sequences deposited in the GISAID database were analysed. For all three single amino acid positions (E340, R682, and V1128), the reference amino acids were present in > 99.9% of sequences. The variants E340A, R682W and V1128F were detected in <0.002% of sequences in the GISAID database.

Sotrovimab neutralization of variants in SARS-CoV-2 pseudotyped virus

In neutralisation testing using a SARS-CoV-2 pseudotyped viruses with spike mutations R682W and V1128F, sotrovimab had EC50 values similar to wild type (< 2-fold change in EC50 relative to wild type). E340A conferred reduced susceptibility to sotrovimab and VIR-7832 (>100-fold change in EC50) indicating that E340A is a monoclonal antibody-resistant mutant (MARM).

Binding of sotrovimab to human Fc receptors and complement component C1q

Study 2020N456792

Sotrovimab was assessed for its ability to bind and activate FcγRs in a series of *in vitro* assays. This study also evaluated the ability of sotrovimab both to promote human natural killer (NK)-cell mediated antibody-dependent cell-mediated cytotoxicity (ADCC) and to promote human monocyte-mediated antibody-dependent cell-mediated phagocytosis (ADCP). An assessment of Fc effector function demonstrated that sotrovimab bound both the H131 and R131 alleles of FcγIIa, FcγIIb and both the F158 and V158 alleles of FcγRIIIa. In addition, binding to complement C1q protein is maintained. ADCC and ADCP assays were performed using CHO cells stably transfected with SARS-CoV-2 spike protein (CHO-CoV-2-Spike) as target cells and sotrovimab was demonstrated to induce NK cell-mediated ADCC

and monocyte mediated ADCP.

In vivo primary pharmacodynamic studies
These were carried out using the Syrian Golden Hamster which is considered to be a robust *in vivo* model of SARS-CoV-2 infection.

Study 2020N457284
This study looked at the effect of exposure to SARS CoV-2 virus of VIR-7831-WT in Golden Syrian hamsters (Mesocricetus auratus). VIR-7831-WT is a version of sotrovimab lacking the LS modification in the Fc region. Antiviral activity and potential for antibody-dependent enhancement of disease (ADE) were assessed as were pharmacokinetics in serum. Both Day -1 prior to infection and Day -2 prior to infection (prophylactic) paradigms of treatment were assessed. In both instances VIR-7831-WT was found to offer protection when using weight loss as a surrogate of disease. This correlated with reductions in total viral load and infectious viral load in the lungs.

Study 2021N471868
This study evaluated the capacity of human IgG1 immunocomplexes to bind hamster splenocytes and the effects of GH-S309, a modified version of the parental antibody S309 containing a hamster IgG2a Fc region, on activity and potential for antibody-dependent enhancement of disease in Syrian golden hamsters. The aim was to determine whether Fc effector function for a human IgG1 like sotrovimab is diminished in hamsters. Binding of immunocomplexes formed by sotrovimab or GH-S309 was examined. The effect of GH-S309 in hamsters challenged with SARS-CoV-2 infection was then determined.

Sotrovimab was found to have substantially lower binding to hamster splenocytes than GH-S309, suggesting lower affinity to host Fcγ receptors. Decreases in viral load, infectious virus titres and improvement in lung pathology were seen in the study with 4 mg/kg of GH-S309.

Study 2021N471990
Syrian golden hamsters were given sotrovimab to determine if there was any evidence of antibody-dependent enhancement of disease (ADE). Hamsters were allocated to 1 of 6 dose groups and were given an intraperitoneal injection of sotrovimab. The control group received diluent only. A further group of hamsters were given a negative control antibody at 30 mg/kg. Two days later they were given SARS CoV-2 virus.

In hamsters given sotrovimab, there was a reduced body weight loss, interpreted as protection from the disease burden following SARS CoV-2 challenge. This was observed at both 5 and 15 mg/kg. Total viral load in lung homogenates from day 4 was reduced at ≥0.5 mg/kg and infectious virus present in the lungs was also reduced at ≥0.5 mg/kg. No enhancement of disease was seen in these measures. Sotrovimab appeared to show a dose-dependent improvement in all measured outcomes. There was no evidence in the data on body weights or lung viral titres to suggest disease exacerbation.

In addition, a preliminary summary of an *in vivo* study in hamsters challenged with the UK (B.1.1.7) SARS-CoV-2 variant was provided in Study 2021N475485. In B.1.1.7 exposed hamsters sotrovimab appeared to reduce disease burden as indicated by protective effects on body weight loss at 5 and 30 mg/kg but not at 0.5 mg/kg. It is noted that the full data from this study (including total lung viral load and lung TCID50) are not yet available.

These studies provide some evidence that sotrovimab is effective in a relevant model of SARS-CoV-2 infection. One limitation with the *in vivo* studies is that the antibody was dosed

prior to intra-nasal infection.

Secondary pharmacodynamics
In vitro and *in vivo* studies were undertaken in order to elucidate if sotrovimab have the potential for antibody-dependent enhancement (ADE).

The *in vitro* studies evaluated enhancement of viral internalisation and replication of SARS-CoV-2 in human cells that express Fc gamma receptor (FcγRs), specifically monocyte-derived dendritic cells (moDCs), peripheral blood mononuclear cells (PBMCs) and U937 macrophage cells and also, as a control, in Vero E6 cells. This approach allowed assessment of Fc-dependent mechanisms of ADE of infection. To evaluate viral entry, replication and cytokine/chemokine release in the presence of sub neutralising concentrations of sotrovimab, of human primary moDS, PBMCs, U937 were first infected with a multiplicity of infection (MOI) of 0.01 of SARS-CoV-2 virus that was pre-complexed with sotrovimab for one hour prior to infection. Cells were analysed for internalisation by immunostaining using n anti-SARS-CoV-2 nucleocapsid antibody at 24 hours.

No entry of SARS-CoV-2 into dendritic, peripheral blood mononuclear or U937 cells was seen in the presence or absence of sotrovimab whereas Vero E6 cells demonstrated internalisation in all conditions evaluated. Sotrovimab showed no enhancement of viral internalisation in any cell type evaluated at any concentration tested compared. Reduced internalisation of SARS-CoV-2 in Vero E6 cells was seen at the highest concentration of sotrovimab indicating that effective virus neutralisation prevented virus entry.

Sotrovimab did not induce antibody-dependent enhancement of SARS-CoV-2 infection in vitro.

In the *in vivo* studies in hamsters, there was no evidence of ADE of the disease, including in 2021N471868 which was performed with the hamster surrogate antibody and where full Fc effector function is expected.

Safety pharmacology
Safety pharmacology endpoints are described under toxicity and were included in the repeat-dose study in cynomolgus monkeys. No test article-related changes in safety pharmacology endpoints were seen in cynomolgus monkeys following IV infusion of sotrovimab at up to 500 mg/kg/dose (5/sex/group).

Pharmacodynamic drug interactions
Study 2021n456694 assessed the combination of sotrovimab with remdesivir, which inhibits viral infection by targeting the viral polymerase, leading to a reduction in viral replication. No interference between the two products was observed.

Study 2021n466415 assessed the combination of sotrovimab with bamlanivimab, a recombinant IgG1 antibody which binds to the SARS-CoV-2 spike receptor binding domain blocking viral attachment to the human ACE2 receptor. Sotrovimab did not interfere with the effects of bamlanivimab.

Study 2021N477024 determined the neutralisation activity of sotrovimab and bamlanivimab individually and in combination against variants of concern and variants of interest in SARS-CoV-2 live virus and pseudotyped virus assays. The effects were evaluated using a SARS-CoV-2 nano luciferase reporter virus encoding nano luciferase in place of the viral ORF7. The variants tested were the following live virus isolates; wild type (USA-WA1/2020 (wild

type), B.1.1.7 (alfa), B.1.351 (beta), P.1 (gamma), and the pseudo typed virus included the B.1.351, P.1, B.1.526 as well as B.152, R.2, B.1.1.427/B.1.1.429 and A.23.1 which bamlanivimab was inactive against at the maximum concentration tested (7000 ng/ml). Sotrovimab alone neutralised all variants tested similarly to wild-type and the combination of sotrovimab and bamlanivimab resulted in an additive effect.

Study 2021N466466 reported effects of the combination of sotrovimab with bamlanivamab against pseudotype variants and the possibility of cross-resistance between these if used as combined agents. Sotrovimab and bamlanivamab were found not to be cross-resistant against the variants tested.

Pharmacokinetics
In studies 2020N456711 and 2021N466078 two ELISA methods were developed for the measurement of sotrovimab in monkey serum.

The ELISA method in the qualification study 2020N456711 detected levels of sotrovimab in monkey serum by use of spectrophotometry and the horseradish peroxidase substrate, tetramethylbenzidine. The formal GLP-compliant validation study was reported as Study 2021N466078. It was concluded that for the measurement of sotrovimab in money serum the assay was considered suitable as it met validation acceptance criteria over the assay range between 50.0 to 5000 ng/ml. The method was free of a matrix effect and was specific and shown to be robust, with no hook effect. The maximum dilution factor was 16,666-fold. It was shown to be stable under storage conditions tested.

The detection of antibodies to sotrovimab in monkey serum was evaluated in Studies 2020N456799 and 2020N466255. Anti-sotrovimab antibodies (ADA) were evaluated using an electrochemiluminescence (ECL) method on an Meso-Scale Discovery (MSD) platform (2021N466255) in samples from the 2-week monkey toxicity study. The method was successfully validated and is considered suitable for its intended use.

Absorption
Study 2020N4556684 characterised serum pharmacokinetics and immunogenicity of sotrovimab when given once at a dose (IV) of 5 mg/kg to cynomolgus monkeys weighing 2.17-2.62 kg on the day they were dosed. Blood was taken from monkeys prior to dosing at day 0 then at regular intervals up to day 56. Results found the mean half-life was 17.7 days, the volume of distribution at steady state was 89.6 ml/kg and the Cmax in serum was 121 µg/ml. No marked sex differences in PK parameters were observed and no ADA's were detected in this study.

Distribution
Distribution of sotrovimab was evaluated in Study 2021N472605. This study sought to evaluate whether modification of the antibody ("LS" modification in the Fc domain) could lead to enhanced mucosal distribution which, if this occurred in the lungs, could be a potential advantage as this may be a main site of action. The study was done in 6 female cynomolgus moneys and compared the distribution of two versions of the antibody, one being sotrovimab as intended for clinical use and the other termed VIR-7831-WT, being the antibody without the modifications of the Fc region in sotrovimab.

Results suggested that the LS modification increases the binding of sotrovimab to FcRn and results in increased distribution of the antibody to the pulmonary bronchi compared to the VIR-7831-WT antibody which lacks this LS mutation.

Metabolic, excretion, pharmacokinetic drug interaction, or other pharmacokinetic studies

No such studies have been done.

Toxicology

Tissue cross reactivity studies

Two tissue cross reactivity studies were done, one in tissues from cynomolgus monkeys (Study 2020n457086) and the other in tissues from adult humans (Study 2020n456662). These studies were performed to identify any off-target binding of the antibody as if so, safety studies may seek to address whether there is any biological consequence to such binding. As the intended target was the virus, there was no expectation of any cross reactivity. These studies were carried out in accordance with Good laboratory Practice (GLP). The studies did not detect any binding of sotrovimab to monkey or human tissues.

Study 2021n468478 assessed binding of sotrovimab in a human embryofetal plasma membrane and secreted protein cell array. Sotrovimab bound to its intended target, SARS-CoV-2-spike protein but not to any of the human embryofetal proteins tested.

Repeat-dose toxicity

Study 2021N468234

One IV repeat dose general toxicity study was performed to assess the potential toxicity of two doses of sotrovimab at 0 (vehicle control), 50, 150 and 500 mg/kg/dose, 7 days apart. The reversibility, persistence, or delayed occurrence of any toxicities were evaluated following a 105-day recovery period. The main study dosing phase animals were necropsied on Day 15 and the recovery animals were necropsied on Day 120. Sotrovimab was well tolerated under the current study, at doses of up to 500 mg/kg (NOAEL, no observed adverse effect level). No toxicity was identified in measures of clinical observations, including injection site analyses, body weights, food consumption, body temperature, ophthalmological examinations, haematology, coagulation, serum chemistry or urinalysis. In addition, no toxicity was identified in the safety pharmacology measures (electrocardiography, blood pressure, heart rate, respiration and neurological examinations).

A comparison of the exposure in animals and in humans, based on observed clinical exposures for the proposed 500 mg human dose was provided. Multiples based on Cmax, and AUC (AUCinf in humans) are 62- and 53-fold, respectively

Table 1: Exposure ratios of sotrovimab in monkeys and humans

Study Type Report No. (Study No.)	Dose (mg/kg/dose)	C_{max}[a] (µg/mL)	C_{max} Ratio of Monkey to Observed Human Exposure	Total Exposure AUC[a, b] (µg·day/mL)	AUC Ratio of Monkey to Observed Human Exposure
Monkey (2-weeks) 2021N468234 (TX-7831-0102)	50	1540	7.1	27000	6.6
	150	4740	21.8	95300	23.2
	500	**13500**	**62.2**	**216000**	**52.5**
Human VIR-7831-5001 (214367)	500	217	N/A	4115	N/A

Note: Bold indicates NOAEL.
Key: NA = not applicable.
a = Observed human C_{max} and AUC_{inf} following a single 500 mg intravenous dose in Study VIR-7831-5001.
b = Total Exposure AUC = Sum of $AUC_{0\text{-}168h}$ after Dose 1 and $AUC_{0\text{-}last}$ after Dose 2 (Day 8).

Genotoxicity, carcinogenicity and reproductive and developmental toxicity
No such studies have been done which is in line with regulatory guidance ICHS6 Preclinical safety evaluation of biotechnology-derived pharmaceuticals.

Local tolerance
Study 2021N470452
This was a single dose study to assess local tolerability following intramuscular injection of sotrovimab in minipigs. The study was performed in the Unites States in compliance with Good Laboratory Practice. A single dose of 62.5 mg/ml (250 mg / pig) did not result in any concerns over local tolerability at the injection site. Pigs were monitored for 72 hours after injection at which point they were killed and the injection sites examined. All changes seen at the injection site were attributed to the injection procedure.

Although the current clinical use in humans is with intravenous dosing, it is possible that intramuscular use may follow. There are no findings identified in this study that raise concerns.

Ecotoxicity/Environmental Risk Assessment
In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature monoclonal antibodies are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies were not provided: this is acceptable.

III.6 Discussion on the non-clinical aspects

Pharmacology
Sotrovimab is an IgG1 antibody that binds to an epitope present on the receptor binding domain of the spike protein of SARS CoV-2. It has a dissociation constant of 0.21 nM and was active in *in vitro* assays to inhibit SARS CoV-2 virus at concentrations in the region of 100-200 ng/ml.

Results from the *in vivo* studies are limited. Sotrovimab neutralised SARS-CoV-2 virus in vitro with an EC50 of 100.1 ng/ml and showed activity to reduce disease in a challenge experiment in which hamsters were given sotrovimab prior to being exposed to SARS-CoV-2 infection - sotrovimab reduced effect of viral challenge to reduce body weight and reduced total viral RNA and infectious virus in the lungs. However, the effect of sotrovimab initiated after exposure to virus was not tested, nor was a time-window defined for any benefit of treatment initiated after symptoms developed.

The epitope to which sotrovimab binds has been identified and based on sequence homology appears well conserved in available SARS-CoV2 sequence data. Using both the knowledge of the epitope as well as *in vitro* resistance selection studies, E340 has been identified as a residue of the epitope for which mutations at this site are likely to significantly affect the neutralisation activity of sotrovimab.

Sotrovimab neutralised SARS-CoV-2 live virus: *in vitro* pseudotyped virus assessments indicate that sotrovimab retains activity against the alpha, beta, delta, gamma, kappa, mu and omicron variants.

The modifications to the Fc region did not impede effector functions of sotrovimab and it has anti-viral activity by antibody-dependent cell mediated cytotoxicity and phagocytosis.

With regard to antibody-dependent enhancement (ADE), the risk appears low. There was no evidence of worsening disease *in vivo* in hamsters and no increase in uptake of virus into human cells *in vitro*.

Pharmacokinetics
The data in relation to the pharmacokinetics of sotrovimab is limited, however, it is considered sufficient in line with ICH S6 (R1), as sotrovimab is a monoclonal antibody targeted at a non-endogenous epitope. The biodistribution study provided supports the assumption that the LS mutation enhances the distribution of sotrovimab to the respiratory mucosa.

Toxicology
Development was in line with that required for an antibody that has a non-mammalian target (ICHS6 Preclinical safety evaluation of biotechnology-derived pharmaceuticals). The lack of OECD-GLP-compliance of the toxicity studies is accepted as it is considered that repetition of the general toxicity studies is unlikely to identify new safety findings.

Standalone safety pharmacology studies are not needed where there are appropriate evaluations in general toxicity studies that do not suggest a concern. No changes were noted in vital systems (cardiovascular, nervous and respiratory systems) in cynomolgus monkeys given an intravenous dose of sotrovimab at up to 500 mg/kg. No issues were identified in the general toxicity study that was done with two doses given to monkeys with a 105-day follow up period thereafter. The dose of 500 mg/kg is accepted as a NOAEL (No Observed Adverse Effect Level). The apparent safety margin for the intended clinical dose is estimated at over 50-fold. A clinical risk of hypersensitivity reactions is not predictable from studies in animals. Overall, although there were some antibodies to sotrovimab detected in monkeys, they do not invalidate the conclusions of the general toxicity study.

No genotoxicity, carcinogenicity and development and reproductive toxicology studies have been conducted in line with ICH S6 guidance.

Reproductive and developmental toxicity studies are not required as sotrovimab binds to a foreign target (i.e. the SARS CoV-2 virus). The tissue cross-reactivity studies did not identify any binding in reproductive tissues or the placenta and no signal for concern was identified in the general toxicity study. These data are sufficient to justify the absence of reproductive toxicity studies.

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
A single pivotal clinical study was submitted with this application:

VIR-7831-5001/COMET-ICE - A Phase II/III randomised, multi-centre, double blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalised patients.

Study Description	Early Treatment Outpatient Study	Evaluating Generation 2 drug substance study	Hospitalized Patient Treatment Study	Evaluating Intramuscular Sotrovimab in Early Treatment Outpatient Study	Evaluating Combination Therapy bamlanivimab + sotrovimab in Early Treatment Outpatient Study (Arms Involving sotrovimab)
Study Number	VIR-7831-5001 (214367), (also known as COMET-ICE)	216912 (also known as COMET-PEAK)	INSIGHT Protocol Number: 014/ACTIV-3-TICO (215149)	VIR-7831-5008 (217114), (also known as COMET-TAIL)	J2X-MC-PYAH (PYAH 05), (VIR-7831-5007), (also known as BLAZE-4)
Study Design	Randomized, double-blind, placebo-controlled study to assess the safety and efficacy of sotrovimab	Randomized, double-blind, multicenter study to characterize the safety, tolerability, and pharmacokinetics of sotrovimab Gen2. Study has three parts: Part A is double-blind and evaluates sotrovimab Gen2 or Gen1 administered via IV infusion (500 mg). Part B is open-label and compares sotrovimab Gen2 administered via IV infusion (500 mg) or IM injection (500 mg). Part C of the study is open-label and participants are randomized 1:1 to receive a 500 mg dose of sotrovimab Gen2 material by IV infusion or a 250 mg dose of sotrovimab Gen2 material by IM injection	A Phase III, adaptive, randomized, blinded, multicenter, controlled trial of the safety and efficacy of investigational therapeutics for hospitalized patients with COVID-19	A Phase III randomized, multi-center, open-label study to assess the efficacy, safety, and tolerability of sotrovimab given as IM versus IV.	Randomized, 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 illness. This is a platform protocol and sotrovimab has only been used in combination with bamlanivimab in one arm of the trial.
Population	Adults with confirmed COVID-19 (mild/moderate, early disease with ≤5 days symptoms) at risk of disease progression	Non-hospitalized adults with confirmed COVID-19 (mild/moderate, early disease with ≤7 days symptoms)	Hospitalized adults who have had COVID-19 symptoms less than or equal to 12 days, with or without end-stage organ failure or dysfunction	Participants aged 12 years and older with mild/moderate COVID-19 at high risk of disease progression	Non-hospitalized adults with mild-to-moderate COVID-19 and who had their viral sample for testing collected ≤3 days prior to infusion
Primary Endpoint (s)	Proportion of participants who have progression of COVID-19 through Day 29 as defined as hospitalisation >24 hours for acute management of illness OR death	• Part A: AEs, SAEs, AESIs, 12-lead electrocardiogram (ECG) readings and disease progression events through Day 29 • Part B: Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUC_{D1-8}) in nasopharyngeal (NP) swab samples • Part C: Mean area under the curve (AUC) of SARS-CoV-2 viral load as measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) from Day 1 to Day 8 (AUC_{D1-8}) in nasopharyngeal swab samples	Time from randomisation to sustained recovery, defined as being discharged from the index hospitalisation, followed by being alive and home for 14 consecutive days prior to Day 90	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	Specific to treatment arms involving sotrovimab: Proportion of participants with SARS-CoV-2 viral load greater than log 5.27 on Day 7
Key Secondary Endpoints	• Proportion of participants who have progression of	• Part A, Part B, and Part C: Serum PK of sotrovimab	• All-cause mortality through 90 days of follow-up	• Progression of COVID-19	Specific to treatment arms involving sotrovimab:

Study Description	Early Treatment Outpatient Study	Evaluating Generation 2 drug substance study	Hospitalized Patient Treatment Study	Evaluating Intramuscular Sotrovimab in Early Treatment Outpatient Study	Evaluating Combination Therapy bamlanivimab + sotrovimab in Early Treatment Outpatient Study (Arms Involving sotrovimab)
	COVID-19 through Day 29 as defined by emergency room (ER) visit, hospitalisation for acute management of illness or death at Day 29 • Mean Change in Flu-PRO Plus Total Score (AUC through Day 7) • Time to symptom alleviation using the FLU-PRO Plus • Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8 • Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifested by the requirement for and method of supplemental oxygen at Day 8,	[Gen2] IV and IM and [Gen1] IV • Part A: Occurrence of non-serious AEs and 12-lead ECG abnormalities through Week 12; occurrence of SAEs, AESIs, and disease progression events through Week 24 • Part B and Part C: Occurrence of AEs, SAEs, AESIs, 12-lead ECG abnormalities, and disease progression events through Day 29 • Part B and Part C: Occurrence of non-serious AEs and 12-lead ECG abnormalities through Week 12; occurrence of SAEs, AESIs, and disease progression events through Week 24 • Change from baseline in viral load at all visits through Day 29 as measured by qRT-PCR from saliva and nasal mid-turbinate swabs samples	• Composite of time to sustained recovery and mortality through 90 days of follow-up • Time to discharge for the initial hospitalisation • Days alive outside of a short-term acute care hospital up to Day 90 • Ordinal outcomes, pulmonary+ and pulmonary, on Days 1-7, and pulmonary ordinal outcome on Days 14 and 28 • Clinical organ failure or serious infections defined by development of any one or more of clinical events through Day 28	through Day 29 as defined by: ○ Visit to a hospital emergency room for management of illness OR ○ Hospitalisation for acute management of illness for any duration and for any cause OR ○ Death • Development of severe and/or critical respiratory COVID-19 as manifested by requirement for respiratory support (including oxygen) at Day	• Percentage of participants who experience COVID-19 related hospitalization or death [baseline through Day 29] • Change from baseline to Day 7 in SARS-CoV-2 viral load [Time Frame: baseline, Day 7] • Percentage of participants demonstrating symptom resolution [Time Frame: Day 7] • Percentage of participants demonstrating symptom improvement [Time Frame: Day 7] • Percentage of participants who experience COVID-19 related hospitalization, COVID-19 related emergency room visit, or death [Time Frame: baseline through Day 22] • Pharmacokinetics (PK): mean concentration of LY3819253 and sotrovimab [Time Frame: Day 29] • Safety assessments such as AEs and SAEs
Study Description	**Early Treatment Outpatient Study**	**Evaluating Generation 2 drug substance study**	**Hospitalized Patient Treatment Study**	**Evaluating Intramuscular Sotrovimab in Early Treatment Outpatient Study**	**Evaluating Combination Therapy bamlanivimab + sotrovimab in Early Treatment Outpatient Study (Arms Involving sotrovimab)**
	Day 15, Day 22, or Day 29 • 29-day, 60-day, and 90-day all-cause mortality	(Part A) or NP swab samples (Part B and Part C) • Part B and Part C: Proportion of participants with undetectable viral load at all visits through Day 29 of the study as measured by qRT-PCR from NP swab samples • Part B and Part C: Mean area under the curve of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 5 (AUC_{D1-5}) and Day 1 to 11 (AUC_{D1-11}) • Part B and Part C: Proportion of individuals with a persistently high viral load at Day 8 as assessed via qRT-PCR in NP swab samples		8, Day 15, Day 22, and Day 29 • Mean area under the curve of SARS-CoV-2 viral load in nasal secretions as measured by qRT-PCR from Day 1 to Day 8 (AUCD1-8) • Change from baseline in viral load by qRT-PCR at Day 8 • Proportion of participants with a persistently high SARS-CoV-2 viral load at Day 8 by qRT-PCR • IV and IM sotrovimab pharmacokinetics (PK) in serum	
Number of Participants (Planned)	1360 participants (680 per treatment arm)	• Part A: 40 participants (30 participants in the Gen2 IV arm, 10 participants in the Gen1 IV arm)	1000 participants (500 per treatment arm)	Approximately 1020 participants (340 participants in each of the IM arms, 340	Treatment arms involving sotrovimab: Approximately 100 participants per treatment arm for the bamlanivimab + sotrovimab or placebo

Study Description	Early Treatment Outpatient Study	Evaluating Generation 2 drug substance study	Hospitalized Patient Treatment Study	Evaluating Intramuscular Sotrovimab in Early Treatment Outpatient Study	Evaluating Combination Therapy bamlanivimab + sotrovimab in Early Treatment Outpatient Study (Arms Involving sotrovimab)
		• Part B: 150 participants (75 participants in the Gen2 IV arm, 75 participants in the Gen2 IM arm) • Part C: 150 participants (75 participants in the Gen2 IV arm, 75 participants in the Gen2 IM arm).		participants in the IV arm)	
Treatment	Randomized 1:1 to receive a single, IV dose of sotrovimab (500 mg) Gen 1 or placebo, administered over 60 minutes	• Part A: Randomized 3:1 to receive a single 500 mg IV dose of sotrovimab Gen2 or Gen1, administered over 60 minutes. • Part B: Randomized 1:1 to receive a single 500 mg IV or IM dose of sotrovimab Gen2. Gen2 IV to be administered over 15 minutes • Part C: Randomized 1:1 to receive a single 500 mg IV or 250 mg IM dose of sotrovimab Gen2. Gen2 IV to be administered over 15 minutes	Sotrovimab sub-protocol: Randomized to receive a single, IV dose of sotrovimab (500 mg) Gen1 or placebo, administered over 60 minutes	Randomized 1:1:1 to receive a single IV infusion of sotrovimab Gen2 (500 mg) or IM injection Gen2 (500 mg or 250 mg)	A single treatment on Day 1 700 mg + 500 mg bamlanivimab + sotrovimab Gen2 or placebo.
Study Start (First Subject First Visit)/Status	27 August 2020 (At the recommendation of IDMC, the study has closed to enrolment on 11 March 2021, and all the randomized participants will continue to be followed until their Week 24 visit [end of study] or early withdrawal)	18 February 2021 (study ongoing)	16 December 2020 (01 March 2021 DSMB recommended recruitment in the sotrovimab sub-protocol should cease, and follow-up of participants already randomized is ongoing)	10 June 2021 (Study ongoing)	The combination arms (bamlanivimab + sotrovimab arm) started on 25 January 2021, follow-up is ongoing

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

VIR-7831 (also known as GSK4182136, sotrovimab) is a dual action engineered human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to a highly conserved epitope on the spike (S) protein receptor binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The fragment crystallisable (Fc) domain of sotrovimab includes an LS modification that extends antibody half-life and may also be expected to enhance distribution to the respiratory mucosa.

The clinical pharmacology of sotrovimab has been studied as a secondary objective in the single pivotal study 214367 (COMET-ICE), a first-in-human (FIH) Phase II/III study that assessed the safety, efficacy, and pharmacokinetics (PK) of a single 500 mg intravenous (IV dose of sotrovimab for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalised participants who were at risk of disease progression. Sotrovimab was administered via a 1 hour (hr) IV infusion.

Absorption

No absorption studies have been conducted with sotrovimab. When sotrovimab was administered by IV infusion, Cmax was observed at the end of the infusion with a mean value of 219 µg/mL in the Lead-in phase.

Distribution
Following IV infusion, sotrovimab distributes into a central volume and declines in a multi-exponential manner reflecting distribution and subsequent elimination. In participants with symptomatic COVID-19, the mean Vss, in the Lead-in phase was 8.1 L (CV%: 11.1).

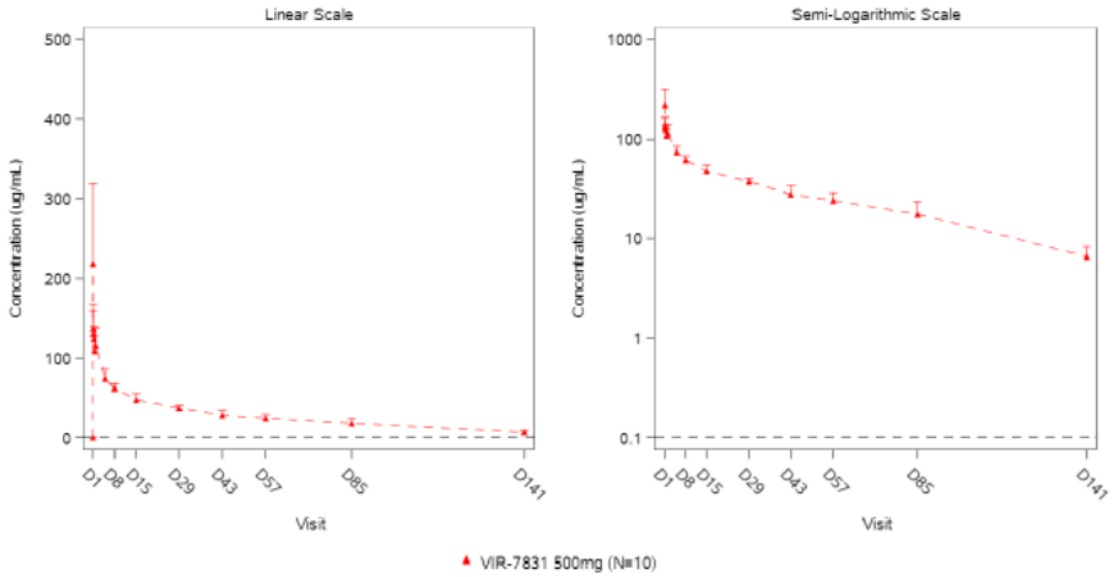
Metabolism
Sotrovimab is an engineered human IgG1 monoclonal antibody degraded by proteolytic enzymes, which are widely distributed in the body and not restricted to hepatic tissue.

Elimination
Sotrovimab systemic clearance is consistent with a half-life extended IgG. Based on NCA of intensive PK data, the mean systemic clearance was 125 mL/day. The median terminal-phase elimination half-life was 48.8 days.

Pharmacokinetics in healthy population
This submission includes complete PK data from the Lead-in phase and approximately 75% of sparse PK data through Day 29 from participants in the Expansion phase.

Serum PK from 10 participants in the Lead-in phase of COMET-ICE (N=10) is available. One participant terminated early on Day 5 due to withdrawal of consent. The mean Cmax of 500 mg sotrovimab was 219 µg/mL following a 1-hr IV infusion. The mean serum level on Day 29 is 37.2 µg/mL. The mean CL and Vss were 125 mL/day and 8.1 L, respectively. The median half-life was 48.8 days. The mean PK profile and parameters are presented in figure 3.

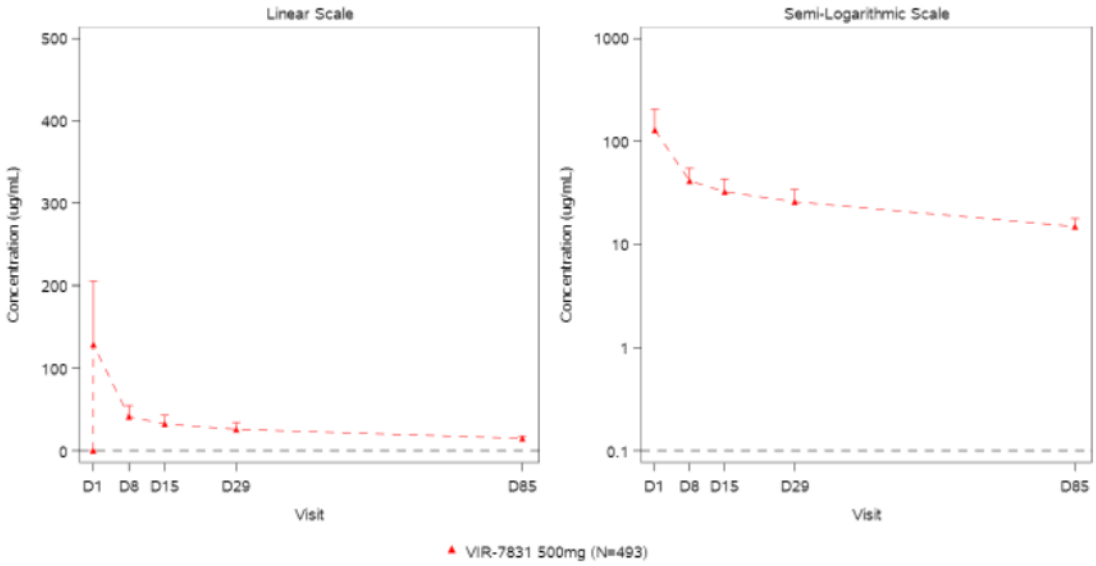
Figure 3: Mean (+standard deviation [SD]) sotrovimab serum concentration-time plots (linear and semi-log): lead-in phase



Source: m5.3.5.1, COMET-ICE CSR, Figure 5.2.
Note: Lower limit of Quantification (LLQ)=0.1 µg/mL. Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist.

Partial sparse serum PK through study Day 29 from 363 participants in the Expansion phase is available to date. The concentration vs. time profile from available Expansion phase PK samples is shown in figure 2.

Figure 4: Mean (+ SD) sotrovimab serum concentration-time plots (linear and semi-log): expansion phase



Sotrovimab PK data from a single pivotal study first in-human (FIH) Phase II/III study showed Cmax was observed at end of the IV infusion. Sotrovimab has mean volume of distribution at steady state of 8.1 L indicating distribution mainly into the central compartment. Sotrovimab has a mean systemic clearance value of 125 mL/day and median terminal-phase elimination half-life of 48.8 days.

Pharmacokinetics in the target population
All sotrovimab PK data is from the target population and no studies were performed in healthy participants.

Objectives:
- To evaluate sotrovimab pharmacokinetics in participants with Coronavirus Disease 2019 (COVID-19) following the administration of a single 500 mg IV dose.
- To investigate the impact of covariates of interest in the studied COVID-19 population (such as baseline characteristics, co-medication) on specific PK parameters (e.g. clearance) in order to identify potential sources of interindividual variability in these parameters.

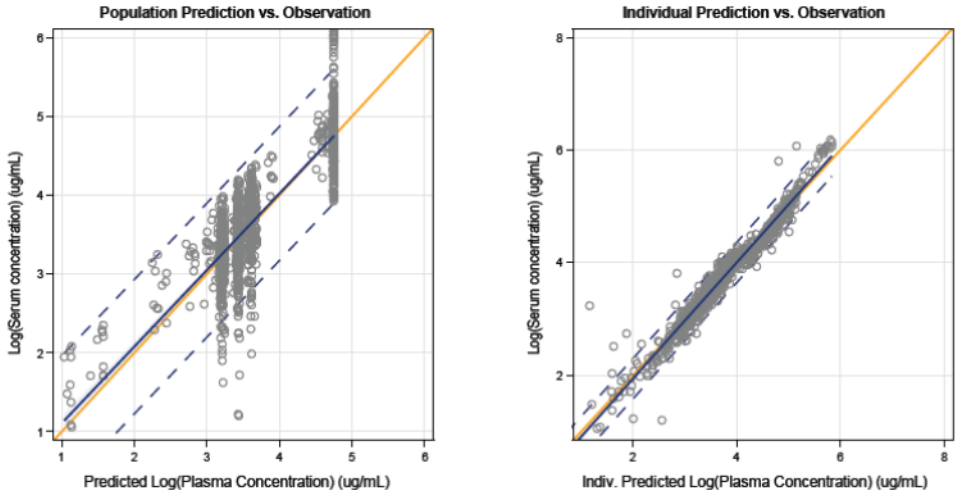
Endpoints:
Non-linear mixed effects model generated estimates for sotrovimab population PK parameters and associated inter-subject variability and residual error:
- Clearance, Volume of distribution (other parameters may be included depending on final model).
- Significant covariates on specific PK parameters, as data permits.

Methodology:
An intravenous (IV) bolus two-compartment pharmacokinetic model was used to describe the PK of VIR-7831 (also known as GSK4182136, sotrovimab) in participants with COVID-19 from study COMET-ICE (214367). Covariate selection was conducted by conventional forward and backward selection based on goodness of fit statistics and parsimony criteria. Overall model goodness of fit was assessed by Visual Predictive Check (VPC) and robust statistical tests.

A simple IV bolus approximation was used for the base model with no random effects, rather than IV infusion model, since for antibodies the rates of distribution and elimination are much less rapid than the duration of infusion (1 hour for COMET-ICE).

Results
Model goodness of fit, as demonstrated by conventional plots and Normal Prediction Distribution Error (NPDE), are adequate and shown in figure 5.

Figure 5: Goodness of fit plots (regression)



Final PK parameters are shown below.

Table 2: Final VIR-7831 (GSK4182136) population PK parameter estimates

Parameter	Units	Description	Estimate	SE	Lower 95% CI	Upper 95% CI	Variability (%)
TVA	/L	Central scalar	0.157	0.006	0.146	0.168	49.5
TVB	/L	Peripheral scalar	0.077	0.002	0.073	0.080	37.5
TVALPH	/day	Distribution rate	0.490	0.031	0.429	0.551	.
TVBETA	/day	Terminal-phase rate	0.016	0.0005	0.015	0.017	.
EPS	NA	Log-residual variance	0.054	0.003	0.048	0.060	23.6
s2b1	NA	Log-BSV variance (A)	0.220	0.030	0.160	0.279	.
s2b2	NA	Log-BSV variance (B)	0.132	0.011	0.111	0.153	.
LNR	NA	Increase in Lead-in Exposure	0.248	0.122	0.009	0.487	.

Pharmacokinetic parameter estimation
Ai = (1+LNR[Lead-in])*TVA exp(-LOG[BWT/87]+0.75*LOG[BMI/32] + b_1)
Bi = (1+LNR[Lead-in])*TVB exp(-LOG[BWT/87]+0.75*LOG[BMI/32] + b_2)
ALPHi = ALPH*exp(0.25*LOG(BWT/87)+0.75*LOG[BMI/32])
BETAi = BETA*exp(0.25*LOG(BWT/87)+0.75*LOG[BMI/32])

CLi = ALPHi BETAi/(Ai BETAi + Bi ALPHAi)
Vdssi = (Ai $BETAi^2$+Bi $ALPHi^2$)/(Ai BETAi + Bi*ALPHi)^2
Thalf(ALPHi) = log(2)/ALPHi (distribution-phase)
Thalf(BETAi) = log(2)/BETAi (terminal-phase)

Between-subject variability
BSV(b1) = SQRT(exp[s2b1] – 1)

Residual error/Between-occasion variability
BOV(%) = SQRT(exp[EPS] – 1)

Parameters are expressed as population estimates (95%CI); SE=Standard error of the estimate, CI = confidence interval, BSV= Between-subject variability, BOV = Between-occasion variability; variability is calculated as 100*SQRT(exp[variance estimate]-1)

Adjusted mean exposure ratio for body weight, BMI, age, ADA, renal and hepatic impairment from this model are presented in Table 2.7. As per the population-PK model, only body weight and body mass index are significant determinants of exposure.

Table 3: Adjusted mean exposure ratios for bodyweight, age, renal and hepatic impairment

Parameter/Ratio	*Estimate*	*Lower*	*Upper*
Lead-in vs. Expansion	1.46	1.17	1.82
BWT 40 vs. 87 kg	1.88	1.50	2.35
BWT 120 vs. 87 kg	0.77	0.70	0.84
BWT 160 vs. 87 kg	0.61	0.51	0.73
BMI 25 vs. 32 kg/m ^2	0.90	0.83	0.98
BMI 35 vs. 32 kg/m ^2	1.04	1.01	1.07
BMI 40 vs. 32 kg/m ^2	1.10	1.02	1.18
Age >=65-84 years vs. 18-64 years	0.89	0.80	0.98
Age >=85 years vs. 18-64 years	0.91	0.66	1.26
Mild (eGFR <90 to >=60 mL/min/1.73 m) vs. Normal	1.05	0.97	1.14
Moderate (eGFR <60 to >=30 mL/min/1.73 m) vs. Normal	1.03	0.86	1.23
Severe (eGFR <30 mL/min/1.73 m) vs. Normal	0.86	0.53	1.39
Mild (Grade 1) vs. Normal	0.97	0.86	1.09
Moderate (Grade 2) vs. Normal	0.99	0.77	1.28
Severe (Grade 3) vs. Normal	0.45	0.23	0.90
ADA Positive (D29) vs. Negative	0.94	0.70	1.26

Linear mixed-effects repeated measures model of log(DV), adjusting for Planned Time, log(WEIGHTBL), AGEGR3, RENIMP and HEPIMP. Geometric mean ratio (95% CI).
DJA17709: C:\Users\dja17709\OneDrive - GSK\Documents\COVID\214367_COMET\SCRIPTS\BATCH_RUN_ALL_01.sas 17JUN2021 00:02

Special populations

No dedicated studies were conducted to evaluate PK of sotrovimab in special populations.

Renal Impairment

Sotrovimab, like other immunoglobulins, is too large to be excreted renally, thus renal impairment is not expected to have any effect on the elimination of sotrovimab. Furthermore, renal impairment was not a covariate of sotrovimab exposure in the population PK analysis. No dose adjustment is required in participants with renal impairment.

Hepatic Impairment

No clinical trials or analyses have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of markers of liver inflammation such as bilirubin and AST as well as mild to moderate elevations in ALT (1.25 to < 5 x ULN) on sotrovimab exposure were assessed via population PK. Hepatic markers were not covariates of sotrovimab exposure. Dose adjustment in participants with hepatic impairment is not expected to be required.

Influence of Ethnicity

In the available data from COMET-ICE, 65.8% were Hispanic or Latino and 34.2% were not Hispanic or Latino. The effect of ethnicity on the PK of sotrovimab were evaluated by population PK analysis. Ethnicity is not covariates of sotrovimab exposure.

Elderly

Although specific studies have not been conducted in the elderly, sotrovimab has been administered to participants aged up to 96 years old (99 participants ≥65 years). The population PK of sotrovimab IV (age range 18 to 96 years) did not identify age as a covariate. No dose adjustment is recommended for elderly participants.

Paediatrics
Sotrovimab IV pharmacokinetics has not been evaluated in paediatric participants (less than 18 years). However, sotrovimab doses in adolescents with a body weight of at least 40 kg can be extrapolated based on efficacious exposure in adult participants. The Sponsor proposes dosing adolescents based on conventional, long-established, allometric assumptions, with scaling powers for volume and clearance of 1.0 and 0.75, respectively. Sotrovimab is not intended for use in participants younger than 12 years or adolescents weighing less than 40 kg.

Pharmacokinetic interaction studies
No interactions studies have been performed which is acceptable. Sotrovimab has a low potential for drug-drug interactions as it is not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Relationship between plasma concentration and effect
COMET-ICE evaluated a single 500 mg IV dose of sotrovimab, therefore no dose-effect relationship has been evaluated. Dose-and/or concentration effect relationships may be evaluated as future data permit.

Immunogenicity summary
Sotrovimab is a human IgG1k mAb that is directed against an epitope on the spike protein of SARS-CoV-2. This bio-therapeutic is intended for use in treating patients who have developed a COVID-19 infection. Due to predicted relatively low risk of immunogenicity against sotrovimab, the immunogenicity risk-based testing plan indicated the use of the industry-standard multi-tiered strategy using validated assays.

Clinical immunogenicity data
During clinical development, immunogenicity was assessed using a risk-based bioanalytical strategy to understand whether ADA responses against sotrovimab impact safety, efficacy, and PK. Based on the low immunogenicity risk for sotrovimab, a validated multi-tier approach anti-sotrovimab antibody method, consisting of screening, confirmation, and titration assays were implemented.

The observed incidence of post-treatment anti-sotrovimab antibodies has been low, with all titre values near the sensitivity limit of the assay (titres ≤160).

In COMET-ICE study, 17 participants confirmed positive at Day 1 (Baseline) for antisotrovimab antibodies with no increase in titre values in subsequent timepoints and, therefore, are not considered treatment-induced ADAs's. Ten participants confirmed positive for anti-sotrovimab antibodies at Day 29 post-treatment time point. Four of these 10 participants were positive for ADA at Baseline with no boosting in titre values at day 29 and therefore are not considered treatment-induced ADA. Six of these 10 participants with positive ADA responses are currently considered to have treatment-induced ADA; two participants were negative for ADA at baseline and 4 participants have not yet had a baseline sample analysed. There were no apparent clinical consequences related to the presence of anti-sotrovimab antibodies. In a preliminary population PK analysis of available data, immunogenicity on Day 29 was not a predictor of serum sotrovimab clearance.

The incidence of treatment-induced anti-sotrovimab antibody responses appears low with relatively low titres and no detectable impact on safety, efficacy, and PK. This clinical evidence aligns with the low immunogenicity risk profile of the molecule. Immunogenicity

will continue to be assessed in the COMET-ICE study.

Dose justification
The current dose of 500mg IV is expected to maintain serum concentrations at 10x adjusted lung tissue EC90 for 28 days in 95% of subjects.

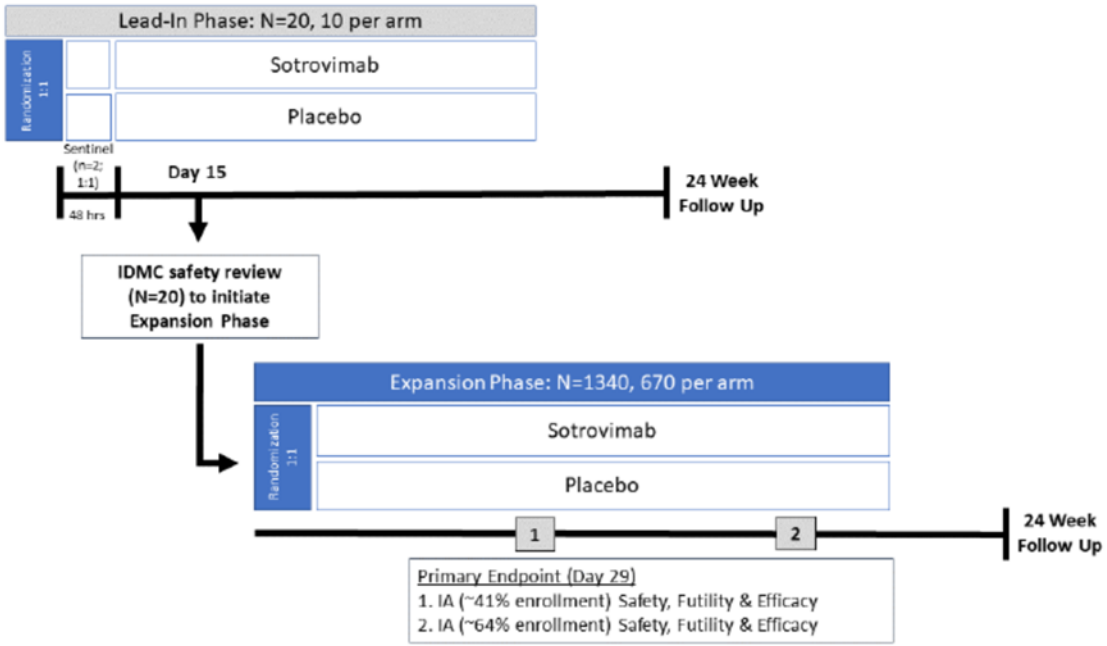
IV.3 Pharmacodynamics
An independent pharmacodynamic study was not submitted.

IV.4 Clinical efficacy
In support of the application, the following was submitted:
COMET-ICE: A Phase II/III randomised, multi-centre, double blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody VIR-7831 for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalised patients.

Study design
Study design
All participants were centrally randomised 1 active :1 placebo using an Interactive Web Response System. Screening assessments were performed within 24 hours before the first dose. Eligible participants were treated in a blinded manner with a single IV dose on Day 1 and followed up to 24 weeks.

The study comprised 2 phases: a first in human study (lead-in phase) and an extension part (phase 2/3 study). The lead in phase included 21 subjects randomised 1:1 to sotrovimab or placebo. Data from the lead in phase are included in the main analysis but given the small proportion of patients in this phase, their inclusion is unlikely to affect the results.

Figure 6: Study design schematic



Two interim analyses to assess efficacy and futility were planned when approximately 41% (IA1) and 64% (IA2) of the required number of participants reached the Day 29 visit.

Dose justification
A single dose of 500 mg was selected for the study 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 GLP monkey toxicology study.

In order to reduce risk to patients (treatment failure, resistance), the dose was selected to ensure that sotrovimab concentrations in lung are maintained at or above levels anticipated to be protective of SARS-CoV-2 infection for the duration of the 28-day treatment window. A dose of 500 mg is expected to maintain serum levels at or above 38.5 μg/mL for the duration of the 28-day treatment period.

Based on PK and pre-clinical studies: the serum trough concentration following a 500 mg dose is expected to result in lung concentrations associated with maximal (>99%) antiviral activity.

Also, a 500 mg dose was anticipated to result in protective levels of sotrovimab in nasopharyngeal secretions (>5 x tissue adjusted EC90 assuming NPS:serum ratio of 0.05). Using a safety factor of 10, the maximum recommended starting dose in humans is approximately 50 mg/kg or a 3000 mg fixed dose. Based on estimated exposures for the proposed 500 mg human dose at the time of protocol writing, the multiples based on the Cmax, and AUC (AUCinf in humans) are 87- and 61-fold, respectively, supporting the proposed clinical dose of 500 mg.

Main inclusion criteria:
Positive SARS-CoV-2 test (RT-PCR or antigen based) AND oxygen saturation in room air ≥94% and onset of COVID-19 symptoms less or equal to 5 days.
In order to be included in the trial, the subjects should furthermore be aged 18 years of age or older and be at risk for COVID-19 progression. For subjects below the age of 55 years, the Applicant has considered the following comorbidities as risk factors for progression to severe COVID-19:

- Diabetes requiring medication
- Obesity (BMI>30 kg/m2 in the original protocol and >35 kg/m2 in amendment 1)
- 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)
- 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).

Participant ≥55 years old, irrespective of co-morbidities (enrolment was targeted to approximately 15% of participants to be >70 years old) could also be included.

Key exclusion criteria:

- Shortness of breath at rest or respiratory distress or requirement of supplemental oxygen.
- Receipt of any COVID-19 vaccine prior to randomisation.
- Severely immunocompromised participants.
- Previous anaphylaxis or hypersensitivity to a mAb.
- Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARSCoV-2 mAb within the last 3 months.

Sample size
Approximately 1360 (680 per arm) participants were to be randomly assigned to study intervention. A total sample size of 1360 would have provided 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 sotrovimab arm, respectively. The minimal detectable efficacy for this design at the Day 29 efficacy analysis was approximately 25% if the disease progression rate was 16% in the placebo arm.

Randomisation
All participants were centrally randomised using an Interactive Web Response System (IWRS). The randomisation was stratified by the following criteria:
1. Age: ≤70 vs. >70 years old
2. Duration of COVID-19 symptoms: ≤3 days vs. 4-5 days
3. Region

Objectives & endpoints
Primary objective:
To evaluate the efficacy of sotrovimab versus placebo in preventing the progression of mild/moderate COVID-19

Secondary efficacy objectives:
- To evaluate the impact of sotrovimab versus placebo on the duration and the severity of COVID-19 clinical symptoms
- To evaluate the efficacy of sotrovimab versus placebo in reducing SARS-CoV-2 viral load
- To evaluate the efficacy of sotrovimab versus placebo in preventing COVID-19 respiratory disease progression
- To evaluate the efficacy of sotrovimab versus placebo in preventing mortality

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.

Secondary efficacy endpoints:
- 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 Hospitalisation for acute management of illness OR Death
- Mean change in FLU-PRO Plus total score comparing sotrovimab vs. placebo (AUC through Day 7)
- Time to symptom alleviation using the FLU-PRO Plus
- Change from baseline in viral load in nasal secretions by quantitative reverse-transcription polymerase chain reaction (qRT-PCR) at Day 8
- 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
- 29-day, 60-day, and 90-day all-cause mortality

Statistical methods
The analysis populations are defined in the table below.

Primary endpoint: An exact Poisson regression analyses was used for the primary analysis adjusted for duration of symptoms, age, and gender. The analysis was conducted in the ITT population. Missing data were imputed using multiple imputation under the assumption missing at random. To investigate the impact of missing values, sensitivity analyses were conducted. Additionally, subgroup analyses on age, symptoms of duration, gender and region were pre-planned and conducted.

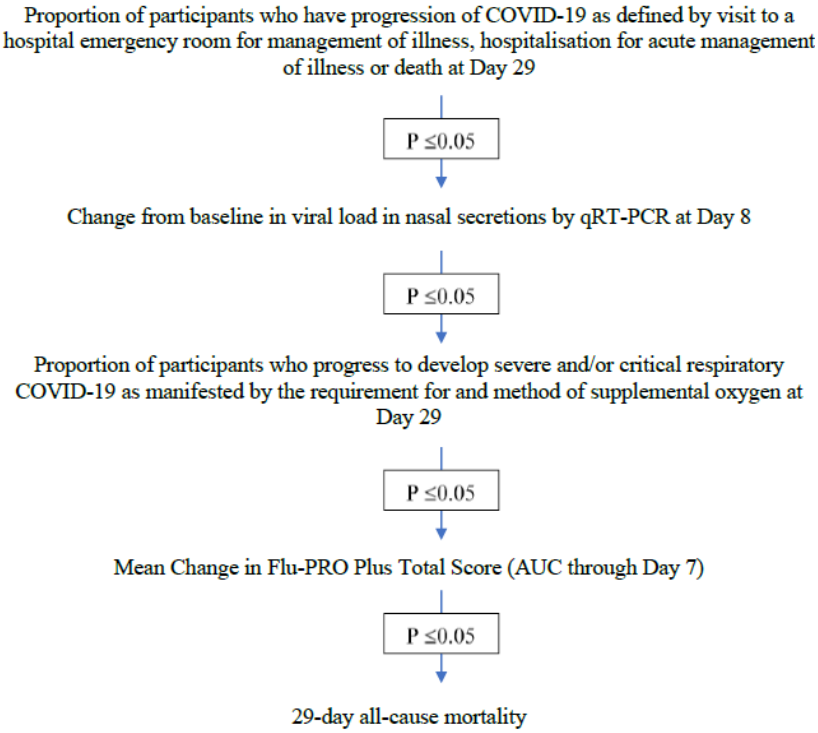
Secondary endpoints: Several secondary endpoints were analysed. Multiplicity has been accounted for by using hierarchical testing with a two-sided alpha of 0.05 (figure below).

Table 4: Analysis population definitions

Participant Analysis Set (Acronym)	Description	Analyses Evaluated
Screened	All participants who were screened for eligibility	Selected Study Population Summaries
Enrolled	All participants who entered the study Note screening failures (who never passed screening even if rescreened) and participants screened were excluded from the Enrolled analysis set, since they did not enter the study	Selected Study Population Summaries
Intent-to-Treat (Interim Analysis) (ITT [IA])	All participants who were randomly assigned to study intervention by 19 January 2021 and therefore had an opportunity to be followed to Day 29 Data were reported according to the randomised treatment	Primary Endpoint
Intent-to-Treat (Day 29 Analysis) (ITT [Day 29])	All participants who were randomly assigned to study intervention in the study. Data were reported according to the randomised treatment	Study Population All Clinical Efficacy Endpoints
Safety (SAF)	All randomised participants who were exposed to study intervention. Participants were analysed according to the treatment they actually received	Selected Study Population Summaries Safety
Per-Protocol (PP)	All participants in the ITT (Day 29) analysis set for whom there were no important protocol deviations that impacted the primary analyses. Data were reported according to the randomised treatment. Specific details of important protocol deviations that impact the primary analysis that would exclude participants from the PP analysis were pre-defined and documented. The PP set will generally not be used for analyses if this analysis set comprises more than 95% or less than 75% of the ITT (Day 29) analysis set.	Primary Efficacy Endpoint
Pharmacokinetic (PK)[a]	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values were considered as non-missing values) Data were reported according to the actual treatment received	PK
Virology[b]	A subset of the ITT (Day 29) analysis set with a central laboratory confirmed quantifiable nasopharyngeal swab at Day 1. Data were reported according to the randomised treatment.	Virology endpoints

a. This report presents Intensive PK data through Week 24 for Lead-in participants and approximately 75% of sparse PK data through Day 29 from participants in the Expansion phase. Full data will be reported in the Week 24 analysis CSR to accommodate timing needed to obtain the data.

Figure 7: Secondary endpoints testing hierarchy



Number of subjects analysed

After 583 subjects had completed the 29-days follow-up, a pre-planned first interim analysis was conducted. Based on a conclusion from an independent data monitoring committee (IDBC), the trial was stopped due to efficacy as was the inclusion of more subjects. The data provided for the current assessment is therefore based on 1057 subjects that were included when the trial was stopped. The subjects have been followed for at least 29 days as this is the duration of follow-up for the primary endpoint. In the sotrovimab arm, 10 out 528 subjects withdrew consent, and in the placebo arm 12 out of 529 subjects withdrew consent. The reasons for withdrawal were similar between treatment arms.

A planned 24-weeks follow-up is yet to be completed but will be provided when available.

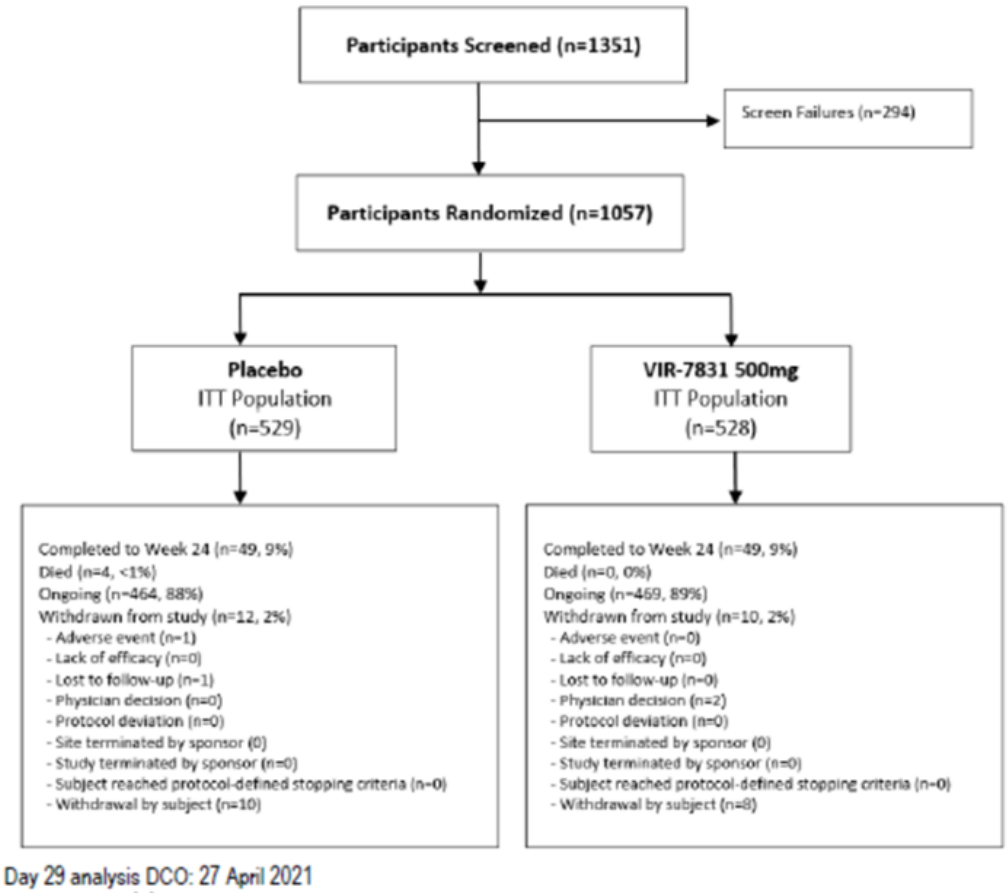
Subject distribution

Table 5: Total number of sites and subjects enrolled per country

Country	Total number of sites enrolling patients	Total number of subjects enrolled
US	45	953
Canada	2	52
Brazil	6	22
Peru	1	1
Spain	3	29

Subject disposition

Figure 8: Participant disposition through day 29 (ITT [day 29])



Demographics
The demographics appeared balanced between study arms.

Table 6: Summary of demographics characteristics at baseline (ITT [day 29])

Parameter	Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)	Total (N = 1057)
Sex			
Female	273 (52%)	299 (57%)	572 (54%)
Male	256 (48%)	229 (43%)	485 (46%)
Age (Years)			
Mean (SD)	52.6 (14.76)	51.6 (15.07)	52.1 (14.92)
Median (Min, Max) [a]	53 (17, 88)	53 (18, 96)	53 (17, 96)
Age Group (Years)			
≤18	4 (<1%)	2 (<1%)	6 (<1%)
19 to 64	417 (79%)	421 (80%)	838 (79%)
≥65	108 (20%)	105 (20%)	213 (20%)
Randomised Age Group Strata (Years)			
≤70	473 (89%)	472 (89%)	945 (89%)
>70	56 (11%)	56 (11%)	112 (11%)
Ethnicity			
Hispanic or Latino	346 (65%)	345 (65%)	691 (65%)
Not Hispanic or Latino	183 (35%)	183 (35%)	366 (35%)
Race (high level)			
American Indian or Alaska Native	2 (<1%)	1 (<1%)	3 (<1%)
Asian	21 (4%)	24 (5%)	45 (4%)
Black or African American	42 (8%)	40 (8%)	82 (8%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	463 (88%)	458 (87%)	921 (87%)
Mixed Race	0	4 (<1%)	4 (<1%)
Weight (kg)			
Mean (SD)	90.05 (21.3)	89.5 (21.5)	89.8 (21.4)
Median (Min, Max)	89 (41, 238.6)	86.6 (49, 183)	87 (41, 238.6)
BMI (kg/m^2)			
Mean (SD)	32.2 (6.6)	32.3 (6.7)	32.3 (6.6)
Median (Min, Max)	31.7 (17.7, 71.2)	31.9 (17.0, 71.1)	31.8 (17.0, 71.2)

In general, the arms of the study appear balanced. In total, 68% subjects had a diagnosis confirmed by nasopharyngeal swab; the other 32% of cases were confirmed by samples taken from the nasal cavity, oral cavity or by taking saliva samples. 85% cases were confirmed by local PCR test; 15% were confirmed by local test for antigen (i.e. lateral flow test).

SARS-CoV-2 diagnosis

Table 7: Summary of SARS-CoV-2 test results at baseline (ITT [day 29])

Parameter	Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)	Total (N = 1057)
Positive Local SARS-CoV2 Test Result[a]			
Yes	529 (100%)	528 (100%)	1057 (100%)
Specimen type[a]			
Nasopharyngeal Swab	376 (71%)	346 (66%)	722 (68%)
Nasal Cavity Swab	134 (25%)	156 (30%)	290 (27%)
Oropharyngeal Swab	9 (2%)	13 (2%)	22 (2%)
Saliva	10 (2%)	10 (2%)	20 (2%)
Other	0	3 (<1%)	3 (<1%)
Method of diagnosis [a]			
RT- PCR	450 (85%)	444 (84%)	894 (85%)
Antigen	79 (15%)	84 (16%)	163 (15%)
Baseline SARS-CoV2 Viral Load (log10 copies/mL) in Nasal Secretions[b]			
N[c]	481	467	948
Mean (SD)	5.919 (2.0823)	5.795 (2.0439)	5.858 (2.0633)
Median (Min, Max)	6.082 (2.873, 9.941)	5.956 (2.873, 9.985)	6.040 (2.873, 9.985)
Not detectable	63 (13%)	64 (14%)	127 (13%)
<2228 copies/mL (<LLQ)	33 (7%)	34 (7%)	67 (7%)
<=log 10^5	84 (17%)	72 (15%)	156 (16%)
>log 10^5 - ≤log 10^6	58 (12%)	64 (14%)	122 (13%)
>log 10^6 - ≤log 10^7	60 (12%)	74 (16%)	134 (14%)
>log 10^7	183 (38%)	159 (34%)	342 (36%)

Abbreviations: RT-PCR = reverse transcriptase polymerase chain reaction;
Day 29 Analysis DCO: 27 April 2021
Source: Table 1.16.
Note: Participants may occur more than once in the list of risk factors and the list of symptoms present.

a. SARS-CoV-2 diagnostic test results for study inclusion, reflecting point-of-care or local laboratory test, and not Baseline viral load at Day 1.
b. Nasopharyngeal swab viral load as measured by the central laboratory. Percentages based on population with detectable SARS-CoV-2 test value at baseline in dataset available to date. Values less than lower limit of detection (LLD=1493 copies/mL) are imputed to 0.5xLLD, detectable values less than lower limit of quantification (LLQ=2228 copies/mL) are imputed to LLQ – (0.5 x [LLQ-LLD]) prior to taking the log 10 value. Percentages are based on the number of non-missing results.
c. The data represent viral load data from >99% of all the expected nasopharyngeal samples through Day 29.

Risk factors for COVID progression and COVID symptoms (ITT)
Risk factors were balanced between treatment arms. 99% subjects had at least one 'risk factor', mostly overweight and over 55yrs age. Most presented within 3 days of onset of symptoms and all within 5 days. The symptoms reported (cough, headache, aches and pains etc.) are typical of those of acute COVID infection.

Concurrent medical conditions at baseline
The most commonly reported co-morbidities (>10% either arm) were hypertension, hyperlipidaemia, gastroesophageal reflux disease; these were balanced between the arms.

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Table 8: Summary of disposition and duration of time on study post-dose

ITT (Day 29)	Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)	Total (N = 1057)
Completed (Overall)[a]	49 (9%)	49 (9%)	98 (9%)
Died	4 (<1%)	0 (0.0)	4 (<1%)
Ongoing	464 (88%)	469 (89%)	933 (88.3%)
Withdrawn from study	12 (2%)	10 (2%)	22 (2.1%)
Primary reason[b] /subreason[c] for study withdrawal			
Adverse event	1 (<1%)	0 (0.0)	1 (<1%)
Lost to follow-up	1 (<1%)	0 (0.0)	1 (<1%)
Physician decision	0 (0.0)	2 (<1%)	2 (<1%)
Withdrawal by participant	10 (2%)	8 (2%)	18 (2%)
Burden of procedure	2 (<1%)	3 (<1%)	5 (<1%)
Participant relocated	1 (<1%)	0 (0.0)	1 (<1%)
Other	7 (1%)	5 (<1%)	12 (1.1%)
Duration of time on study postdose (SAF) [d]	**N=526**	**N=523**	**Total (N = 1049)**
<5 days	1 (<1%)	0 (0.0)	1 (<1)
5 to 10 days	1 (<1%)	1 (<1%)	2 (<1%)
11 to 14 days	1 (<1%)	0 (0.0)	1 (<1)
15 to 29 days	6 (1%)	2 (<1%)	8 (<1)
>29 days	517 (98%)	520 (>99%)	1037 (99%)
>85 days	357 (68%)	360 (69%)	717 (68%)
>141 days	77 (15%)	78 (15%)	155 (15%)
n	522	523	1045
Mean (SD)	103.1 (33.48)	103.7 (32.89)	103.4 (33.17)
Median (Min, Max)	103 (3, 176)	103 (5, 178)	103 (3, 178)

Day 29 analysis: 27 April 2021
Source: Table 1.1, Table 1.4.

a. Participant is considered to have completed the study if he/she completed all visits of the study to Week 24.
b. Participants may have only one primary reason for study withdrawal.
c. Percentages for sub-reasons for study withdrawal may sum to more or less than 100%. Participants may have more than one sub-reason underneath a single primary reason. Participants are not required to indicate sub-reasons.
d. Calculated as min(completion/withdrawal date, data cut date) - date of dosing + 1. Note: The denominator of percentage is the number of participants that received study treatment i.e. number with non-missing duration post-dose.

Protocol deviations
In general, the arms of the study appeared balanced in terms of protocol deviations. At randomisation 299 subjects (28%) were mis-stratified.

Interim analysis
An interim analysis was conducted at approximately 41% of participants enrolled to evaluate futility, efficacy, and safety based on data through Day 29 for participants. The study was stopped due to efficacy and some staff members were unblinded. The staff involved in the day-to-day conduct of study were kept blinded. Hence, efficacy and safety are not considered affected by the interim analysis.

Populations analysed
The intention to treat population comprised 1057 subjects and the PP population 1015 subjects. The number of subjects with virology data at time of submission was 733. The number of participants for each of the analysis populations was consistent across both treatment arms. See table below for the population sets analysed.

Table 9: Population sets (enrolled)

Population[a]	Placebo	Sotrovimab (500 mg IV)	Total
Analysed for Interim Analysis			
ITT [IA]	292	291	583
Analysed for the Day 29 Analysis			
ITT [Day 29]	529	528	1057
Per-Protocol	507	508	1015
Safety (SAF)	526	523	1049
Pharmacokinetic (PK)	0	503	503
Virology[b]	375	358	733

Source: Table 1.9
Day 29 analysis DCO: 27 April 2021
a: Descriptions of each study population as well as the analyses for which it was used are provided in Table 2.
b: This report presents viral load data from approximately 90% of all nasopharyngeal samples through Day 29. Full data will be reported in the Week 24 analysis CSR to accommodate timing needed to obtain the data.

Results

Interim analysis

In the first pre-planned interim analysis, which led the DSMB to recommend termination of enrolment, sotrovimab 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) within 29 days of treatment. The adjusted relative risk ratio of 0.15 (97.24% CI: 0.04, 0.56) indicates the corresponding relative risk reduction of 85%.

Primary endpoint

Thirty out of 529 subjects in the placebo group and 6 out of 528 subjects in the sotrovimab group had an event (hospitalisation more than 24 hours or death). The adjusted relative risk ratio was 0.21 (95% CI: 0.09;0.50) and the corresponding relative risk reduction was 79%. Less than 1% of subjects had missing data and the sensitivity analysis counting these patients as progressions also confirmed efficacy.

Two subjects in the placebo group died compared to none in the sotrovimab group. One subject died due to COVID-19 pneumonia and one subject died due to pneumonia.

The risk difference was 6%.

Table 10: Summary of primary endpoint analyses (ITT [1A] and ITT [day 29])

	Interim Analysis (ITT [IA])		Day 29 Analysis (ITT [Day 29])	
	Placebo N=292	Sotrovimab (500 mg IV) N=291	Placebo N=529	Sotrovimab (500 mg IV) N=528
Progression of COVID-19 through Day 29 as defined by hospitalisation >24 Hours for acute management of illness or Death				
Hospitalised >24 hours for acute management of illness or death, due to any cause	21 (7%)	3 (1%)	30 (6%)	6 (1 %)
Hospitalised >24 hours for acute management of any illness	21 (7%)	3 (1%)	29 (5%)	6 (1%)
Death due to any cause	1 (<1%)	0	2 (<1%) [a]	0
Alive and not hospitalised	270 (92%)	284 (98%)	494 (93%)	515 (98%)
Missing[b, c]	1 (<1%)	4 (1%)	5 (<1%)	7 (1%)
Adjusted relative risk ratio	0.15		0.21	
97.24% CI [d]	0.04, 0.56		0.08, 0.56	
95% CI	0.04, 0.48		0.09, 0.50	
p-value[d]	0.002		<0.001	
Risk difference	-8.05		-6.34	
Adjusted number needed to treat [e]	13		16	

Interim Analysis 1 DCO: 04 March 2021
Day 29 Analysis DCO: 27 April 2021
Source: Table 2.2, and Table 2.3

a. One participant died due to COVID-19 pneumonia and one participant died due to pneumonia.
b. For ITT (IA): 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).
c. For ITT (Day 29): Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 5 placebo participants (2 withdrew consent prior to treatment, 1 withdrew consent on Day 3, 1 withdrew consent on Day 15, 1 was withdrawn due to an adverse event of intermittent nausea on Day 11) and 7 sotrovimab participants (4 withdrew consent prior to treatment, 2 were withdrawn due to physician decision prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
d. Significance level for the Interim Analysis 1 Day 29 α=2.758%.
e. Number of participants needed to treat in order to prevent one additional hospitalisation >24 hour or death by Day 29.

Secondary endpoints

Table 11: Summary of key secondary efficacy results

	Placebo N=529	Sotrovimab (500 mg IV) N=528
Progression of COVID-19 through Day 29 as defined by visit to a hospital ER for management of illness or hospitalisation for acute management of illness or death (ITT [Day 29])		
Hospitalised, ER visit or death, due to any cause	39 (7%)	13 (2%)
Hospitalised for acute management of any illness, any duration	29 (5%)	7 (1%)
ER visit due to any cause	10 (2%)	6 (1%)
Death due to any cause	2 (<1%)	0
Alive and not hospitalizsed and no ER visit	485 (92%)	508 (96%)
Missing[a]	5 (<1%)	7 (1%)
Adjusted relative risk reduction (95% CI)	66% (37%, 81%)	
p-value	<0.001	
Change from Baseline in Viral Load in Nasal Secretions by qRT-PCR on Day 8 (Virology) (N=733)		
Baseline (log 10 copies/mL)		
n	375	358
Mean (standard deviation)	6.652 (1.6732)	6.554 (1.6248)
Day 8 viral load (log 10 copies/mL)		
n [b]	305	294
Mean (SD)	4.284 (1.3455)	4.039 (1.2071)
LS Mean Change from Baseline (SE)	-2.357 (0.0598)	-2.589 (0.0606)
95% CI	-2.475, -2.240	-2.708, -2.470
LS Mean Difference (SE)	-0.232 (0.0851)	
95% CI	-0.399, -0.065	
p-value	0.007	
Progression to develop Severe and/or Critical Respiratory COVID-19 (Day 29) (ITT [Day 29])		
Progression to Severe/Critical Respiratory COVID-19 Status, n (%)		
No progression[c]	495 (94%)	514 (97%)

	Placebo N=529	Sotrovimab (500 mg IV) N=528
Any progression[d]	28 (5%)	7 (1%)
Category 2: Low flow nasal cannulae/face mask (severe)	12 (2%)	7 (1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	10 (2%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	4 (<1%)	0
Death	2 (<1%)	0
Missing[a]	6 (1%)	7 (1%)
Adjusted relative risk reduction (95% CI)	74% (41%, 88%)	
p-value	0.002	
Mean Change in FLU-PRO Plus Total Score (AUC through Day 7) (ITT [Day 29])		
n	399	412
Mean (standard deviation)	-1.98 (-2.20, -1.76)	-3.05 (-3.27, -2.83)
LS Mean Difference (SE)	-1.07 (0.158)	
95% CI	-1.38, -0.76	
p-value	<0.001	
All-cause mortality (up to Day 29) (ITT [Day 29])[e]		
Deceased (n, %)	2 (<1%)	0
Alive at Day 29 (n, %)[f]	518 (98%)	521 (99%)
Censored at study withdrawal[g]	9 (2%)	7 (1%)

Day 29 Analysis DCO: 27 April 2021

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 5 placebo participants (2 withdrew consent prior to treatment, 1 withdrew consent on Day 3, 1 withdrew consent on Day 15, 1 was withdrawn due to an AE of intermittent nausea on Day 11) and 7 sotrovimab participants (4 withdrew consent prior to treatment, 2 were withdrawn due to physician decision prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Number of participants with analysable data at Day 8.
c. All participants' status at admission is Category 1: Room air.

<u>Progression of COVID-19 through day 29 as defined by visit to a hospital emergency room for management of illness or hospitalisation for acute management of illness or death due to any cause</u>

Thirteen (2%) participants in the sotrovimab arm compared with 39 (7%) in the placebo arm met the secondary endpoint of progression of COVID-19 through Day 29 as defined by visit to a hospital ER for management of illness or hospitalisation for acute management of illness (any duration) or death due to any cause.

<u>Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8</u>

The mean decline from baseline in viral load at Day 8 was greater in sotrovimab-treated participants compared to that in placebo-treated participants (p=0.007).

<u>Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 through Day 29 (ITT [Day 29])</u>

Treatment with a single 500 mg dose of sotrovimab resulted in a reduction in the risk of severe and/or critical respiratory COVID-19 through Day 29 when compared with placebo (adjusted relative risk reduction: 74% [95% CI: 41%, 88%]; p = 0.002). No participants treated with sotrovimab required high-flow oxygen, oxygen via a non-rebreather mask, or mechanical ventilation through Day 29. Ten participants treated with placebo required oxygen support via highflow nasal cannulae, non-rebreather mask or non-invasive ventilation, and 4 participants in the placebo arm required mechanical ventilation. This secondary endpoint on progression of subjects has been met.

Table 12: Summary of proportion of participants who progress to severe and/or critical respiratory COVID-19 by visit at day 8, day 15, day 22, or day 29 (ITT[day29])

	Day 8		Day 15		Day 22		Day 29	
	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)
Number of Participants	529	528	529	528	529	528	529	528
Progression to Severe/Critical Respiratory COVID-19 Status, n (%)								
No Progression [a]	506 (96%)	515 (98%)	497 (94%)	515 (98%)	495 (94%)	514 (97%)	495 (94%)	514 (97%)
Any Progression [b]	20 (4%)	6 (1%)	28 (5%)	6 (1%)	28 (5%)	7 (1%)	28 (5%)	7 (1%)
Category 2: Low flow nasal cannulae/face mask (severe)	7 (1%)	6 (1%)	12 (2%)	6 (1%)	12 (2%)	7 (1%)	12 (2%)	7 (1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	11 (2%)	0	11 (2%)	0	10 (2%)	0	10 (2%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	1 (<1%)	0	4 (<1%)	0	4 (<1%)	0	4 (<1%)	0
Death	1 (<1%)	0	1 (<1%)	0	2 (<1%)	0	2 (<1%)	0
Missing	3 (<1%)	7 (1%)	4 (<1%)	7 (1%)	6 (1%)	7 (1%)	6 (1%)	7 (1%)

Day 29 analysis DCO 27 April 2021
Source: Table 2.2.6
a. All participants status at admission is Category 1: Room air.
b. "Any progression" defined as either death or Category 2, 3, or 4. 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. Participants could have received oxygen at home or in hospital.
Note: Participants with progression are counted in the worst-case progression that they have reported up to the relevant time point.

Mean change from baseline in FLU-PRO plus total score (AUC through Day 7)
Completed FLU-PRO Plus questionnaires were available from more than 80% of participants on Day 1; by Day 21, completed questionnaires were available from approximately 50% of participants in both treatment groups. The mean decreases in total score were statistically significantly greater for sotrovimab vs. placebo based on AUC0-7, 0-14 and 0-21 but the large amount of missing data creates uncertainty around these estimates.

Table 13: Summary of average change from baseline (AUC) of COVID-19 related illness as measured by total score of the FLU-PRO Plus at day 7, day 14, day 21 (ITT [day 29])

		Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)
AUC to Day 7	n	399	412
	Mean (95% C.I.)	-1.98 (-2.20, -1.76)	-3.05 (-3.27, -2.83)
	Difference (95% C.I.)	-1.07 (-1.38, -0.76)	
	p-value	<0.001	
AUC to Day 14	n	373	385
	Mean (95% C.I.)	-7.04 (-7.51, -6.58)	-9.40 (-9.85, -8.94)
	Difference (95% C.I.)	-2.35 (-3.00, -1.70)	
	p-value	<0.001	
AUC to Day 21	n	345	379
	Mean (95% C.I.)	-13.34 (-14.03, -12.64)	-16.42 (-17.09, -15.76)
	Difference (95% C.I.)	-3.09 (-4.05, -2.12)	
	p-value	<0.001	

Day 29 analysis DCO: 27 April 2021

Time to sustained (≥48 hours) symptom alleviation through day 21 (ITT [Day 29])
In the ITT (Day 29) analysis, a larger number of participants in the sotrovimab arm (14.5%) versus placebo arm (5.9%) reported sustained symptom resolution by Day 7. Over the first 21 days, the difference between the arms was statistically significant (logrank test p-value= 0.002) with 41% in the sotrovimab arm and 34% in the placebo arm reporting symptom resolution at Day 21.

Table 14: Summary and analysis of time to sustained (≥ 48 hours) symptom alleviation as measured by FLU-PRO Plus (ITT [day 29])

		Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)
Day 7	Number of participants with event	31 (6%)	76 (14%)
	Number of participants censored	4 (<1%)	6 (1%)
	Number of participants without event	494 (93%)	446 (84%)
	Probability of having event (95% CI)	5.9% (4.2%, 8.3%)	14.5% (11.8%, 17.9%)
Day 14	Number of participants with event	104 (20%)	164 (31%)
	Number of participants censored	5 (<1%)	6 (1%)
	Number of participants without event	420 (79%)	358 (68%)
	Probability of having event (95% CI)	19.8% (16.7%, 23.5%)	31.4% (27.6%, 35.6%)
Day 21	Number of participants with event	178 (34%)	214 (41%)
	Number of participants censored	351 (66%)	314 (59%)
	Number of participants without event	0	0
	Probability of having event (95% CI)	34.0% (30.1%, 38.2%)	41.0% (36.9%, 45.4%)
	Sotrovimab 500 mg vs. Placebo		
	Log-Rank p-value	0.002	

Day 29 analysis DCO: 27 April 2021
Source: Table 4.5
Note: Analysis was performed using a log-binomial model, adjusting for region (North America, Europe, South America, Asia and Rest of the World), duration of symptoms (≤3 days vs. ≥4 days), age (≤70 vs. >70) and gender (male, female). Available data were used in the analysis as collected, regardless of the occurrence of intercurrent events.

All-cause mortality at day 29

Up to day 29, no deaths occurred in the sotrovimab group vs. 2 in the placebo group among those with data.

Table 15: Summary of time to all-cause mortality at day 29 (ITT [day 29])

Parameter	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)
Number of Participants		
Deceased	2 (<1%)	0
Alive at Day 29[a]	518 (98%)	521 (99%)
Censored at Study Withdrawal[b]	9 (2%)	7 (1%)

Day 29 analysis DCO 27 April 2021
Source: Table 2.30
a. Participants alive at end of follow-up were censored at Day 29, respectively.
b. Censored at study withdrawal includes 11 of the 12 missing participants for the primary endpoint (randomised but not treated [sotrovimab 5; placebo 2]; 1 participant treated with sotrovimab withdrew consent at Day 5; 3 participants in the placebo arm who withdrew without hospitalisation >24 or death at Day 3, Day 11, and Day 15) and an additional 1 participant treated with sotrovimab who was hospitalised and subsequently withdrew at Day 15 and 4 participants in the placebo arm who were hospitalised and subsequently withdrew consent at Day 16 (two participants), Day 24 (1 participant), and Day 26 (1 participant). One of the sotrovimab participants missing for the primary endpoint (was randomised and not treated and had an early withdrawal visit conducted late at 28 days after randomisation); as this participant had vitals collected, mortality status could be determined as alive at Day 29.
Note: Log-rank test was not performed due to insufficient number of events.

Subgroup analysis on serostatus at baseline
Overall at baseline:

- 70% of participants were seronegative
- 19% of participants were seropositive
- 11% participants with unknown antibody status due to missing serology results

All data appeared balanced across treatment arms.

Table 16: Summary of primary and key secondary efficacy endpoints by serostatus at baseline (positive, negative)

Serostatus at Baseline	Positive		Negative	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	97	105	375	365
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death) (ITT [Day 29])				
Progression Status, n (%)				
..Hospitalised >24 hours or Death, due to any cause	4 (4%)	2 (2%)	26 (7%)	4 (1%)
Hospitalised >24 hours for acute management of any illness	4 (4%)	2 (2%)	25 (7%)	4 (1%)
Death due to any cause	0	0	2 (<1%)	0
..Alive and not hospitalised >24 hours	93 (96%)	103 (98%)	345 (92%)	360 (99%)
..Missing[a]	0	0	4 (1%)	1 (<1%)
Relative risk ratio	0.49		0.16	
95% CI	0.09, 2.64		0.06, 0.45	
Risk difference	-2.99		-8.21	
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n[b]	34	41	250	233
LS mean change from baseline (standard error)	-2.610 (0.1752)	-2.619 (0.1610)	-2.346 (0.0658)	-2.592 (0.0675)
95% CI	(-2.954, -2.266)	(-2.935, -2.303)	(-2.476, -2.217)	(-2.724, -2.459)
Difference (standard error)	-0.009 (0.2312)		-0.245 (0.0935)	
95% CI	(-0.463, 0.445)		(-0.429, -0.062)	
Mean Change from Baseline in FLU-PRO Plus Total Score (AUC through Day 7) (ITT [Day 29])				
n	77	78	283	288
LS mean (standard error)	-2.05 (0.253)	-3.16 (0.252)	-1.89 (0.132)	-2.89 (0.131)
95% CI	(-2.54, -1.55)	(-3.66, -2.66)	(-2.14, -1.63)	(-3.14, -2.63)
Difference (standard error)	-1.11 (0.356)		-1.00 (0.185)	
95% CI	(-1.81, -0.42)		(-1.37, -0.64)	

Day 29 analysis DCO: 27 April 2021. Source: Table 152.01, Table 152.02, Table 154.01
a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 4 placebo participants (1 withdrew consent prior to treatment, 1 withdrew consent on Day 3, 1 withdrew consent on Day 15, 1 was withdrawn due to an adverse event of intermittent nausea on Day 11) and 1 sotrovimab participant (withdrew consent prior to treatment).
b. Number of participants with analysable data at Day 8.

<u>Hospitalisation for >24 hours or death due to any cause</u>
In the seropositive subgroup, 2/105 (2%) participants in the sotrovimab arm met the primary endpoint compared to 4/97 (4%) participants in the placebo arm [51% reduction in risk (RR 0.49, 95% CI (0.09, 2.64)]. Notably, the two participants in the sotrovimab arm who met the primary endpoint were hospitalised for events potentially unrelated to COVID-19 (diabetic foot ulcer, non-small cell lung cancer). There were no deaths in participants seropositive at baseline in either arm.

In the seronegative subgroup, 4/365 (1%) participants in the sotrovimab arm progressed met the primary endpoint compared to 26/375 (7%) in the placebo arm [84% reduction in risk (RR 0.16, 95% CI (0.06, 0.45)]. Of the four sotrovimab treated participants who met the primary endpoint, one participant progressed due to an event potentially unrelated to COVID-19 (small intestinal obstruction). Of the 26 seronegative participants in the placebo arm who met the primary endpoint, two met the endpoint due to death.

SARS-CoV-2 viral load by baseline serostatus

In the seropositive subgroup, decline in SARS-CoV-2 viral load was similar between the sotrovimab arm and placebo, where the difference in viral load for sotrovimab compared with placebo was -0.009 log10 copies/mL at Day 8.

In the seronegative subgroup, the decline in SARs-CoV-2 viral load was greater in the sotrovimab arm, with a difference in viral load for sotrovimab compared with placebo of -0.245 log10 copies/mL at Day 8.

FLU-PRO Plus data by baseline serostatus

In the subgroup analysis the FLU-PRO Plus by serostatus, the mean decrease in total score in FLU-PRO Plus as measured by AUC0-7 was greater in the sotrovimab arm regardless of baseline serostatus than in the placebo arm.

IV.5 Clinical safety

Patient exposure

The primary evaluation of sotrovimab safety is based on the data from one clinical placebo-controlled study to evaluate the efficacy and safety of sotrovimab as monotherapy (COMET - ICE).

A total of 1057 participants were included in the COMET-ICE study, and 1049 participants were exposed and comprise the safety population (sotrovimab: 523; placebo: 526) for the current procedure. Of the 1049 participants included in the COMET-ICE safety dataset, 1037 participants were followed through >29 days and 717 (68%) have been followed for >85 days. Of the 523 participants in the sotrovimab arm included in the COMET-ICE safety dataset, 520(>99%) participants were followed through >29 days and 360 (69%) have been followed for >85 days.

Safety data is also provided for 399 participants from three other on-going supportive studies yet owing to the differences in study populations, administration method, and/or use of sotrovimab in combination with other mAbs, safety data has not been integrated from these additional studies.

Table 17: Summary of studies used to characterise sotrovimab safety profile

Study	Available Data	Number of participants with mild-to moderate COVID-19 at risk of progression or death (N) (randomised and received sotrovimab)
COMET-ICE (analysis data cut-off DCO: 27 April 2021)	Primary evaluation of safety data in support of marketing authorization application (MAA) Application	N= 1049 (sotrovimab [Gen1]=523)
Supportive safety information from ongoing studies		
COMET-PEAK-(DCO: 12 May 2021)	Additional blinded safety data from Council for International Organization of Medical Sciences (CIOMS) reports in patients with mild to moderate COVID-19	Part A:N=30 (IV: Gen1 or Gen 2) Part B: N=86 (IV or IM Gen 2) (sotrovimab = 116)
ACTIV-3 TICO (DCO: 18 March 2021)	Additional unblinded safety summary from hospitalised patients including exposure	N=360 (sotrovimab [Gen 1]=182)
BLAZE-4 (DCO: 17 March 2021)	Available unblinded safety data from non-hospitalised patients including exposure (combination only, no sotrovimab monotherapy arm)	N= 202 (sotrovimab [Gen 2] + bamlanivimab=101)

Summary of disposition and duration of time on study post-dose are shown in table 20.

Baseline demographic, including age and comorbidities in the COMET-ICE patient population was balanced between the placebo and sotrovimab arm. Of the total safety population, 213 subjects were above 65 years of age. Type and number of risk factors were also balanced between the treatment arms, with greater than 99% of participants in both treatment arms having at least one risk factor associated with COVID-19 progression.

Table 18: Summary of disposition and duration of time on study post-dose

ITT (Day 29)	Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)	Total (N = 1057)
Completed (Overall)[a]	49 (9%)	49 (9%)	98 (9%)
Died	4 (<1%)	0 (0.0)	4 (<1%)
Ongoing	464 (88%)	469 (89%)	933 (88.3%)
Withdrawn from study	12 (2%)	10 (2%)	22 (2.1%)
Primary reason[b] /subreason[c] for study withdrawal			
Adverse event	1 (<1%)	0 (0.0)	1 (<1%)
Lost to follow-up	1 (<1%)	0 (0.0)	1 (<1%)
Physician decision	0 (0.0)	2 (<1%)	2 (<1%)
Withdrawal by participant	10 (2%)	8 (2%)	18 (2%)
Burden of procedure	2 (<1%)	3 (<1%)	5 (<1%)
Participant relocated	1 (<1%)	0 (0.0)	1 (<1%)
Other	7 (1%)	5 (<1%)	12 (1.1%)
Duration of time on study postdose (SAF) [d]	**N=526**	**N=523**	**Total (N = 1049)**
<5 days	1 (<1%)	0 (0.0)	1 (<1)
5 to 10 days	1 (<1%)	1 (<1%)	2 (<1%)
11 to 14 days	1 (<1%)	0 (0.0)	1 (<1)
15 to 29 days	6 (1%)	2 (<1%)	8 (<1)
>29 days	517 (98%)	520 (>99%)	1037 (99%)
>85 days	357 (68%)	360 (69%)	717 (68%)
>141 days	77 (15%)	78 (15%)	155 (15%)
n	522	523	1045
Mean (SD)	103.1 (33.48)	103.7 (32.89)	103.4 (33.17)
Median (Min, Max)	103 (3, 176)	103 (5, 178)	103.0 (3, 178)

Source: m5.3.5.1, COMET-ICE CSR Table 1.1, Table 1.4.
Day 29 analysis DCO: 27 April 2021

a. Participant is considered to have completed the study if he/she completed all visits of the study to Week 24.
b. Participants may have only one primary reason for study withdrawal.
c. Percentages for sub-reasons for study withdrawal may sum to more or less than 100%. Participants may have more than one sub-reason underneath a single primary reason. Participants are not required to indicate sub-reasons.
d. Calculated as min(completion/withdrawal date, data cut date) - date of dosing + 1. Note: The denominator of percentage is the number of participants that received study treatment i.e. number with non-missing duration post-dose.

Adverse events

Overview of Adverse Events are shown in table 21. The overall rate of AEs was similar in the two groups. AE occurred in 123 (23%) in the placebo arm and in 114 (22%) in the sotrovimab arm; 9 (2%) and 8 (2%) respectively were considered drug related (see table 22).

The adverse event profile is typical for this type of product.

Table 19: Adverse event overview (SAF)

	Placebo (N=526) n (%)	Sotrovimab (500 mg IV) (N=523) n (%)
Any AE	123 (23%)	114 (22%)
AEs related to study treatment	9 (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 AE	36 (7%)	15 (3%)
Any SAE	32 (6%)	11 (2%)
SAEs related to study treatment	2 (<1%)	0
Fatal SAEs	4 (<1%)	0
Fatal SAEs related to study treatment	0	0
Any Infusion-Related Reaction (IRR)[b]	6 (1%)	6 (1%)
IRRs related to study treatment[d]	3 (<1%)	0
IRRs leading to permanent discontinuation of study treatment	0	0
IRRs leading to dose interruption/delay[c]	0	0

Day 29 Analysis DCO: 27 April 2021

Source: m5.3.5.1, COMET-ICE CSR, Table 3.2 Table 3.26, Table 3.14 and Listing 11

a. A participant was permanently discontinued from completion of study 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 (PTs) for AESIs, which include pyrexia, chills, dizziness, dyspnoea, pruritus, rash, infusion related reaction and only includes events that started within 24 hours of start of study treatment.

c. AEs leading to dose interruption in the sotrovimab were 2 AEs of infusion site extravasation in 2 participants leading to temporary dose interruption in the sotrovimab arm; however, they did not lead to dose discontinuation. For both events, the infusion was able to be completed, and the time to complete the infusion, including interruption, was 1 h 17 min and 1 h 8 min, respectively.

d. IRRs related to study treatment were reported in 3 participants in the placebo arm: dizziness, pruritus and rash.

Table 20: Summary of drug-related adverse events by overall frequency (SAF)

System Organ Class Preferred Term	Placebo (N=526)	Sotrovimab 500 mg IV (N=523)
ANY EVENT	9 (2%)	8 (2%)
Skin and subcutaneous tissue disorders		
Any event	2 (<1%)	2 (<1%)
Rash	1 (<1%)	1 (<1%)
Pruritus	1 (<1%)	0
Skin reaction	0	1 (<1%)
Gastrointestinal disorders		
Any event	2 (<1%)	1 (<1%)
Nausea	1 (<1%)	1 (<1%)
Dyspepsia	1 (<1%)	0
General disorders and administration site conditions		
Any event	1 (<1%)	2 (<1%)
Infusion site erythema	1 (<1%)	0
Infusion site pain	0	1 (<1%)
Infusion site swelling	1 (<1%)	0
Pain	0	1 (<1%)
Investigations		
Any event	1 (<1%)	2 (<1%)
Blood bicarbonate decreased	1 (<1%)	1 (<1%)
C-reactive protein increased	1 (<1%)	1 (<1%)
Aspartate aminotransferase increased	0	1 (<1%)
Blood alkaline phosphatase increased	0	1 (<1%)
Gamma-glutamyltransferase increased	0	1 (<1%)
Oxygen saturation decreased	0	1 (<1%)
Nervous system disorders		
Any event	1 (<1%)	2 (<1%)
Dizziness	1 (<1%)	0
Dysgeusia	0	1 (<1%)
Headache	0	1 (<1%)
Infections and infestations		
Any event	2 (<1%)	0
COVID-19 pneumonia	2 (<1%)	0
Psychiatric disorders		
Any event	0	1 (<1%)
Insomnia	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders		
Any event	1 (<1%)	0
Cough	1 (<1%)	0

Day 29 analysis DCO: 27 April 2021

A summary of common adverse events is displayed below. The most common AE (≥ 1%) consisted of COVID -19 pneumonia, headache, nausea and diarrhoea and accounts for 68/237 (29%). The majority of AEs in the sotrovimab treatment arm were Grade 1 or 2. There was a lower proportion of participants with severe (using the DAIDS grading) Grade 3 or 4 AEs in the sotrovimab arm than in the placebo arm (3% vs. 7%, respectively). Diarrhoea was more frequent in the sotrovimab arm (all Grade 1 or 2). Numerically more participants in the sotrovimab arm met laboratory criteria for hepatocellular injury ([(ALT/ALT ULN) / (ALP/ALP ULN)]) ≥5 and ALT ≥3xULN) (3/511 [<1%] in the placebo arm vs 6 /516 [1%] in the sotrovimab arm). See Laboratory findings also.

Table 21: Summary of common (≥1%) adverse events by preferred term in either arm (SAF)

Preferred Term	Placebo (N=526) n (%)	Sotrovimab (500 mg IV) (N=523) n (%)
Any event	123 (23%)	114 (22%)
COVID-19 pneumonia	22 (4%)	5 (<1%)
Headache	11 (2%)	4 (<1%)
Nausea	9 (2%)	5 (<1%)
Diarrhoea	4 (<1%)	8 (2%)

Day 29 analysis DCO: 27 April 2021

The rate of drug-related AEs was low and similar between sotrovimab and placebo (2% for each). There were 8 in the sotrovimab arm with 10 drug-related AEs, all of which were DAIDS Grade 1 (7 events) or 2 (3 events).

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

Infusion-related reactions and hypersensitivity
Systemic infusion related reactions (IRRs), including hypersensitivity, were defined by a pre-specified custom MedDRA list of PTs for AEs occurring within 24 hours of initiation of infusion. Patients were observed for 2 hours after infusion for immediate IRRs. Systemic IRRs that started within 24 hours of study treatment were observed at similar rates with sotrovimab and placebo.

The frequency of infusion-related reactions (IRR) including hypersensitivity are comparable across treatment groups. IRR was represented equally in the two arms (6 participant (1%) in each arm) (see table 24). Hypersensitivity SMQ narrow, of grade 1 (mild) or grade 2 (moderate), were reported in 9 participants in the sotrovimab arm and 5 in the placebo arm (table 25). All infusion-related reactions (IRRs) reported in the COMET-ICE were Grade 1 and 2 and no cases of anaphylaxis were reported following infusion of sotrivimab.

Table 22: Summary of infusion-related reactions by overall frequency (SAF)

System Organ Class Preferred Term	Placebo (N=526) n (%)	Sotrovimab (500 mg IV) (N=523) n (%)
Any event	6 (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	3 (<1%)	1 (<1%)
Dizziness	3 (<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%)

Source: m5.3.5.1, COMET-ICE CSR, Table 3.4 and Table 3.23
Note: Infusion-related reactions (including hypersensitivity) are defined using a selection of preferred terms and only include events that started within 24 hours of study treatment (or AEs that started on Day 1 or Day 2 if AE onset time was missing).

Table 23: Incidence of hypersensitivity SMQ narrow (SAF)

Preferred Term	Placebo (N=526)		Sotrovimab (500 mg IV) (N=523)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hypersensitivity SMQ Narrow				
Any event	5 (<1%)		9 (2%)	
Rash	4 (<1%)	0	3 (<1%)	0
Dermatitis	1 (<1%)	0	0	0
Dermatitis contact	0	0	1 (<1%)	0
Skin reaction	0	0	1 (<1%)	0
Hypersensitivity	0	0	1 (<1%)	0
Multiple allergies	0	0	1 (<1%)	0
Infusion-related reaction	0	0	1 (<1%)	0
Bronchospasm	0	0	1 (<1%)	0

Day 29 analysis DCO: 29 April 2021

More hypersensitivity reactions were observed in the sotrovimab group n=9 compared to placebo n=5 and thus hypersensitivity may be related to the administration of sotrovimab. Eight of these hypersensitivity related events took place beyond 24 hours following dosing.

Antibody-dependent enhancement of disease

Regarding adverse events related to antibody-dependent enhancement of disease. A broad array of PTs was reviewed within the renal, cardiac, and pulmonary SOCs to identify any potential events that might be suggestive of antibody-dependent enhancement.

Potential pulmonary ADE events: The incidence of these AEs was higher in the placebo arm (30 [6%]) than in the sotrovimab arm (6 [1%]) and there were more severe events in the placebo arm compared to the sotrovimab arm.

Potential renal ADE events: All renal events occurred in the placebo arm. Thus, there is no

evidence of a renal ADE based on a review of renal AEs. However, elevations in creatinine values (increase from baseline) seemed to be more frequent in the sotrovimab.

Potential cardiac ADE events: Cardiac events occurred in 5 patients in sotrovimab arm and in 2 patients in the placebo arm. The events are in different MedDRA higher-level term groups (tachycardia, palpitations, myocardial ischaemia, cardiomegaly, cardiac deconditioning).

Serious adverse events and deaths
No deaths were reported in the sotrovimab arm of the study. Four deaths were reported in the placebo arm, of which two occurred before day 29 and two after day 29. Three were due to pneumonia and one due to respiratory failure.

Table 24: Listing of deaths (SAF)

Age Band (years)	Days from Dose to Onset of Fatal AE	Duration of SAE (i.e. duration in days from onset to death)	Adverse event (preferred term)	AE possibly causally related to study drug?	Primary cause of death	Death related to disease under investigation (per PI)?
Placebo						
70-79	5	1	COVID-19 pneumonia	No	COVID-19 pneumonia	Yes
70-79	4	15	Pneumonia	No	Pneumonia	N/S
70-79	8	27	COVID-19 pneumonia	No	COVID pneumonitis	Yes
70-79	12	23	Respiratory failure	No	Respiratory failure	N/S

Day 29 analysis DCO:27 April 2021
Source: Listing 15
N/S denotes not specified in the PI narrative

Serious AEs were numerically more common in the placebo arm. Most SAEs were hospitalisations due to COVID-19.

Table 25: Serious adverse events overview (SAF)

	Placebo (N=526) n (%)	Sotrovimab (500 mg IV) (N=523) n (%)
Number of Participants with SAEs	32 (6%)	11 (2%)
Number of SAEs	37	11
Number of Participants with Fatal SAEs	4	0
Number of Participants with Treatment-Related SAEs	2	0

Below is the listing of serious adverse events in the sotrovimab arm (table 29). Three participants had COVID-19 pneumonia, two participants had diverticulitis, two participants had diabetic complications relating to dysregulated diabetes. Single reports of SAEs were: non-small cell lung cancer, small intestinal obstruction, myocardial ischaemia and adenocarcinoma pancreas.

Table 26: Listing of serious adverse events (SAF)

Age Band (Years)	Time to SAE from dose (days)	SAE (preferred term)	SAE possibly causally related to study drug? (per PI)	SAE related to disease under investigation (per PI)?[a]
Sotrovimab 500 mg IV				
80-89	90	Diverticulitis	No	N/S
30-39	50	Diverticulitis	No	N/S
30-39	5	Diabetes mellitus	No	N/S
70-79	1	COVID-19 pneumonia	No	Yes
50-59	13	Non-small cell lung cancer	No	N/S
60-69	22	Small intestinal obstruction	No	N/S
90-99	19	COVID-19 pneumonia	No	Yes
90-99	40	Adenocarcinoma pancreas	No	N/S
50-59	19	Diabetic foot	No	N/S
60-69	47	Myocardial ischaemia	No	Yes
60-69	2	COVID-19 pneumonia	No	Yes

Source: m5.3.5.1, COMET-ICE CSR, Listing 7 and Listing 16

a. N/S denotes not specified in the PI narrative.

Laboratory findings

A summary of chemistry changes from baseline is provided in Table 29.

The majority of participants had no change in haematology or chemistry parameters or had normalisation post-baseline. Changes to outside the normal range occurred at similar frequencies in the arms. Most increases were Grade 1 or Grade 2.

Changes in clinical chemistry parameters (from baseline to day 29) to outside the normal range occurred at a similar frequency between the arms. Overall, 33 participants (6.3%) in the sotrovimab treatment arm and 20 participants (4%) in the placebo arm had laboratory results of Grade 3-4.

Overall, 44 had increase in creatinine values that were categorised as severe or life threatening. These severe increases were balanced across the arms, but life-threatening increase happened in one participant in the sotrovimab arm whereas it happened in 5 participants in the placebo arm.

Table 27: Summary of chemistry changes from baseline (SAF)

Parameter Increase	Placebo (N=526) n (%)	Sotrovimab (500 mg IV) (N=523) n (%)
Alanine Aminotransferase (IU/L) / ALT or SGPT, High		
n	511	516
No Increase	461 (90%)	469 (91%)
Increase to Grade 1	45 (9%)	38 (7%)
Increase to Grade 2	5 (<1%)	8 (2%)
Increase to Grade 3	0	1 (<1%)
Increase to Grade 4	0	0
Increase to Grades 1 to 4	50 (10%)	47 (9%)
Increase to Grades 2 to 4	5 (<1%)	9 (2%)
Increase to Grades 3 to 4	0	1 (<1%)
Aspartate Aminotransferase (IU/L) / AST or SGOT, High		
n	514	519
No Increase	487 (95%)	502 (97%)
Increase to Grade 1	24 (5%)	13 (3%)
Increase to Grade 2	3 (<1%)	2 (<1%)
Increase to Grade 3	0	2 (<1%)
Increase to Grade 4	0	0
Increase to Grades 1 to 4	27 (5%)	17 (3%)
Increase to Grades 2 to 4	3 (<1%)	4 (<1%)
Increase to Grades 3 to 4	0	2 (<1%)
Bilirubin (umol/L) / Total Bilirubin, High		
n	514	519
No Increase	509 (>99%)	510 (98%)
Increase to Grade 1	4 (<1%)	7 (1%)
Increase to Grade 2	1 (<1%)	0
Increase to Grade 3	0	1 (<1%)
Increase to Grade 4	0	1 (<1%)
Increase to Grades 1 to 4	5 (<1%)	9 (2%)
Increase to Grades 2 to 4	1 (<1%)	2 (<1%)
Increase to Grades 3 to 4	0	2 (<1%)
Creatinine (umol/L) / Creatinine, High		
n	514	519
No Increase	442 (86%)	444 (86%)
Increase to Grade 1	2 (<1%)	2 (<1%)
Increase to Grade 2	52 (10%)	47 (9%)
Increase to Grade 3	13 (3%)	25 (5%)
Increase to Grade 4	5 (<1%)	1 (<1%)
Increase to Grades 1 to 4	72 (14%)	75 (14%)
Increase to Grades 2 to 4	70 (14%)	73 (14%)
Increase to Grades 3 to 4	18 (4%)	26 (5%)
Potassium (mmol/L) / Potassium, High		
n	514	519
No Increase	503 (98%)	506 (97%)
Increase to Grade 1	4 (<1%)	6 (1%)
Increase to Grade 2	5 (<1%)	5 (<1%)
Increase to Grade 3	2 (<1%)	2 (<1%)
Increase to Grade 4	0	0
Increase to Grades 1 to 4	11 (2%)	13 (3%)
Increase to Grades 2 to 4	7 (1%)	7 (1%)
Increase to Grades 3 to 4	2 (<1%)	2 (<1%)
Potassium (mmol/L) / Potassium, Low		
n	514	519
No Increase	506 (98%)	514 (>99%)
Increase to Grade 1	6 (1%)	5 (<1%)
Increase to Grade 2	2 (<1%)	0
Increase to Grade 3	0	0
Increase to Grade 4	0	0
Increase to Grades 1 to 4	8 (2%)	5 (<1%)
Increase to Grades 2 to 4	2 (<1%)	0
Increase to Grades 3 to 4	0	0

Summary of hepatobiliary abnormalities are shown in table 30. Few participants (n=15) in either arm had ALT results that were ≥3 ULN (<1% in the placebo arm and 2% in the sotrovimab arm). Six patients in the sotrovimab arm met the laboratory criteria for

hepatocellular injury vs three in the placebo arm.

Table 28: Summary of hepatobiliary abnormalities (SAF)

Laboratory Criteria[a]	Placebo N = 526 n (%)	Sotrovimab (500 mg IV) N = 523 n (%)
n	511	516
ALT ≥3xULN	5 (<1%)	10 (2%)
ALT ≥5xULN	0	1 (<1%)
ALT ≥8xULN	0	0
ALT ≥10xULN	0	0
ALT ≥20xULN	0	0
n	511	516
ALT ≥3xULN and BIL ≥2xULN[b]	0	0
n	504	509
ALT ≥3xULN and INR >1.5[c]	0	0
n	511	516
ALT ≥3xULN and BIL ≥2xULN [c] and (ALP <2xULN)	0	0
n	511	516
Hepatocellular injury [d]	3 (<1%)	6 (1%)
n	511	516
Hepatocellular injury [d] and BIL ≥2xULN [b]	0	0

ALT: alanine aminotransferase; ALP: alkaline phosphatase; BIL: total bilirubin; INR: International Normalised Ratio; ULN=upper limit of normal.
Source: m5.3.5.1, COMET-ICE CSR, Table 3.33
n = number of participants with results post-Baseline
a: Participants may be counted in more than one category.
b: If direct bilirubin is available, then direct bilirubin as a portion of total bilirubin must be >=35% when total bilirubin is >=2xULN, in order to satisfy the criteria. Bilirubin value is on or up to 28 days after ALT value.
c: INR value is on or up to 28 days after ALT value.
d: Hepatocellular injury is defined as ([ALT/ALT ULN]/[ALP/ALP ULN]) ≥ 5 and ALT ≥3xULN. ALT and ALP values must occur on the same day.

No clinically meaningful changes were noted in electrocardiogram or vital parameters with sotrovimab treatment.

Safety data from other studies
Three clinical studies in addition to the pivotal COMET-ICE study have been conducted with sotrovimab for the treatment of COVID-19. In these studies, approximately 399 participants have received sotrovimab as monotherapy or in combination with bamlanivimab. The studies are: COMIT-PEAK, ACTIV-3-TICO and BLAZE-4.

COMET PEAK provides only SAE data (blinded). 30 participants were enrolled in Part A and no SAEs were reported in these participants. In Part B, 86 participants have been enrolled and 6 SAEs were reported. The 6 SAE occurred in 4 patients, see table 31.

In the ACTIV-3-TICO study there was no evidence of a difference between treatment groups

of a composite safety endpoint of Grade 3/4 AEs, SAEs, organ failure, serious infections, and death. This composite endpoint occurred in (19.2%) participants in the sotrovimab group, compared with 44 (24.7%) in the placebo group. Potentially life-threatening infusion reactions was observed in two participants who received sotrovimab. In total, 19 participants died; 11 in the sotrovimab group and 8 in the placebo group.

In BLAZE-4 based on the available safety data, no SAEs, IRRs related to study treatment, or AEs that led to discontinuation have been reported. Follow-up is ongoing.

Table 29: Listing of serious adverse events reported in the sotrovimab arm of supportive studies

Age Band (years)	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-B) (DCO12 May 2021)					
60-70	2 days	Grade 3 COVID-19 pneumonia	No	Yes	Symptoms of Grade 3 fatigue; Grade 2 events of myalgia, arthralgia, malaise, and headache; and Grade 1 events of fever, cough, sore throat, shortness of breath, inability to walk, loss of taste and chills at screening. Two days after receiving sotrovimab, the participant was admitted to the Intensive Care Unit due to a Grade 3 worsening COVID pneumonia. Test results were negative for pulmonary emboli. The participant was treated with supplemental oxygen, dexamethasone, remdesivir, enoxaparin, oxygen, Symbicort, and acetaminophen. The participant did not require mechanical ventilation. The event resolved six days later.
40-50	1 day	Grade 2 COVID-19 pneumonia	No	Yes	Serious criteria included hospitalization. The participant was treated with dexamethasone, bemiparin sodium and levofloxacin. The outcome of covid-19 pneumonia was not recovered/not resolved
50-60	4 days	Grade 3 coronavirus pneumonia	No	Yes	Low oxygen saturation and a pathological lung auscultation detected, x-ray and blood exam performed. The outcome of coronavirus pneumonia was not recovered/not resolved
50-60	2 days	Grade 3 dehydration	No		Medical history of smoking. Entered the study with Grade 3 fever, cough, productive cough, myalgia, arthralgia, fatigue, malaise, headache, vomiting, nausea, and chills. oxygen saturation dropped from 96 to 89% and she was treated with high flow oxygen. Medical records indicated that the participant was diagnosed with bilateral pneumonia, acute hypoxic respiratory failure requiring BIPAP/Hi-flow via nasal cannula, hypokalemia, transaminitis, and elevated BNP. The participant was additionally treated with furosemide and famotidine. The outcome of dehydration and bilateral pneumonia was not recovered/not resolved.
	2 days	Grade 4 bilateral pneumonia	No		
	2 days	Grade 4 acute hypoxic respiratory failure	No		

Safety in special populations

Fertility, pregnancy and lactation

No participant became pregnant during the COMET-ICE study. One patient in the ACTIV-3-TICO study was pregnant, but no data are provided. Hence, there are no clinical data on human fertility, pregnancy or lactation. Human immunoglobulin G (IgG) as sotrovimab can potentially pass the placental barrier from mother to foetus.

Elderly

Adverse events and SAEs were assessed in COMET-ICE participants who were >55, 55-64, 65-74, 75-84, and ≥85 years of age. The number of adverse events in each age-group is shown below.

Table 30: Number of adverse events by participant in elderly population

	Age <55 (n/N) (%)	Age 55-64 (n/N) (%)	Age 65-74 (n/N) (%)	Age 75-84 (n/N) (%)	Age 85+ (n/N) (%)
Placebo	55/272 (20%)	38/146 (26%)	24/71 (34%)	6/30 (20%)	0/7 (0%)
Sotrovimab (500 mg IV)	55/281 (20%)	33/138 (24%)	18/76 (24%)	5/23 (22%)	3/5 (60%)

Renal or hepatic impairment

The incidence of AEs was similar between both the treatment arms for each of the renal

impairment category (kidney function was defined as normal for eGFR ≥90 mL/min, mildly impaired for eGFR <90 to ≥60 mL/min, moderately impaired for eGFR <60 to ≥30 mL/min, and as severely impaired for eGFR <30 mL/min). Overall, AEs were more common in participants with moderate or severe renal impairment.

Table 31: Number of adverse events in participants with renal or hepatic impairment (SAF population)

	Placebo n/N (%)	Sotrovimab (500 mg IV) n/N (%)
Maximum Renal Impairment (% based on all participants)		
Normal	62/296 (21%)	67/324 (21%)
Mild	41/174 (24%)	34/152 (22%)
Moderate	10/27 (37%)	8/22 (36%)
Severe	3/5 (60%)	1/2 (50%)
Maximum Hepatic Grade (% based on all participants)		
Normal	22/419 (5%)	9/421 (2%)
Grade 1	10/43 (23%)	10/42 (24%)
Grade 2	2/10 (20%)	2/8 (25%)
Grade 3	1/2 (50%)	0/1 (0%)
Grade 4	1/1 (100%)	0/1 (0%)

Immunological events
A multi-tiered approach to evaluating anti-sotrovimab antibodies consisting of screening, confirmation and titration assays was implemented.

Currently, the observed incidence of post-treatment ADAs has been low, with all titre values near the sensitivity limit of the assay (titres ≤160); available results from approximately 75% of the participants up to Day 29 are provided in Table 34. Ten participants confirmed positive for anti-sotrovimab antibodies at Day 29 (4 of the 10 were also positive at baseline).

Table 32: Number of confirmed positive immunogenicity results for sotrovimab through day 29 (ITT [day 29])

Visit	Sotrovimab (500 mg IV) (N=528) n (%)
Day 1	17/375 (5%)
Day 29	10/391 (3%)

Source: m5.3.5.1, COMET-ICE CSR, Table 2.34
Note: Summary presents the number of confirmed positive out of the total number of screening samples.

Safety related to drug-drug interactions and other interactions
No pharmacokinetic drug interaction studies have been conducted with sotrovimab to date. Only in vitro assessments have been performed.

Discontinuation due to AES
Two AEs (Grade 1) infusion site extravasations were reported in two participants and led to temporary dose interruption in the sotrovimab arm, both events resolved within 10 minutes and did not led to dose discontinuation. No participants experienced an AE that permanently stopped the infusion of sotrovimab or placebo. One patient in ACTIV-3-TICO had the infusion stopped after 21 minutes due to IRR.

Sotrovimab was administered as a single dose. Thus, no treatment interruption besides incomplete infusion due to AEs was possible per definition.

Post marketing experience
No data has been provided. Data will be presented for authorities as part of routine pharmacovigilance.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
Overall, the benefit of exposure to sotrovimab by reducing hospital encounters is considered to outweigh risk for adult subjects who have symptomatic COVID infection of recent onset and so the study may be considered to support a positive benefit-risk profile for the recipient.

The development of variants of the COVID-19 takes two forms: (i) those that develop in the sotrovimab epitope and (ii) those that develop in the receptor binding domain outside of the sotrovimab epitope.

For those variants that develop in the sotrovimab epitope: change at positions 337 and 340 are associated with much reduced affinity of sotrovimab for the receptor binding domain; these changes may result in decreased efficacy, yet this would be very difficult to confirm / demonstrate given the natural history (for most) of an infection that resolves over 10 days after exposure. Since efficacy is retained for most recipients and since harm is limited mostly to hypersensitivity-type reactions that may be managed by simple intervention, then decreased efficacy for some, whilst unfortunate, is not considered to have a large consequence on the overall benefit-risk profile.

For those variants that develop in the receptor binding domain outside of the sotrovimab epitope: the *in vitro* data suggests that sotrovimab retains activity. It is not known if such variants can survive and be passed on to others. This may be pursued by a post-approval exercise within a conditional licence.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19

infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID infection.

Xevudy has been authorised with a Conditional Marketing Authorisation (CMA). In addition, a Regulation 174 authorisation is in place to supply Northern Ireland.
The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Drug substance and drug product release specifications: The applicant should commit to re-evaluate the specification limits and to provide a revised justification of specification when further manufacturing data becomes available (including batches from the new Samsung Biologics SBL manufacturing site). This re-evaluation should also incorporate additional batch results obtained with the new pseudotype neutralization assay. Moreover, the re-evaluation of specification limits should address the shelf life limits for HMW species based on additional manufacturing experience and further stability data becoming available.	After 30 batches of DS and DP, or after 2 years by the latest.
Drug product analytical methods: Missing information in the validation report for the polysorbate 80 HPLC-ELSD the method provided, including intermediate precision, reproducibility as well as laboratory equivalence between PPD and GSK Parma should be included in the PLGB dossier.	Estimated date by Q1 2022
Drug substance and drug product stability The applicant should provide additional stability data.	Estimated date by Q1 2022
Drug product manufacturing A post-authorization commitment has been raised regarding the DP manufacturing – to be addressed by the company once 30 batches have been manufactured: -the purpose of the bioburden reduction filter and the nature of the raw materials and the process operations are understood and it is noted that levels measured so far are well below the proposed limit, indicating that it could be significantly reduced. However, given the limited manufacturing experience, it can be accepted that the current limit of ≤ 50 CFU/100 ml for the BDP sampled prior to the bioburden reduction filtration can be PLGB 19494/0301 - 0001 grant of marketing authorisation - page 5 of 6 retained on the basis that it will be re-evaluated and, if appropriate reduced, once 30 batches have been manufactured	
Final quality sequence GSK is requested to provide a final sequence with any remaining quality dossier updates to MHRA as agreed	End of January 2022
GSK-UK will provide the week 24 clinical study report for the pivotal COMET-ICE study (to include safety analyses, PK data, immunogenicity data) and the final virology study report	30 April 2022
The company will provide variants by visit for positions 340 and 337 within 6 weeks post approval.	14 January 2022
The company will provide quality control analyses of nucleotide variant sequences at amino acid positions 700-707	31 March 2022
The applicant will provide additional PK data and any further e-r analysis	Q2 2022
The applicant will provide PK data from adolescent population and final	Q2 2024

CSR	
The company will develop a study protocol for post authorisation safety study to further characterise the emergence of viral variants in patients treated with sotrivimab. The study should be broadly reflective of how the product is used clinically and mainly focuses on use in immunocompromised patients. The company will submit an acceptable study protocol within 6 weeks of approval.	Week commencing 10th January 2022
The company will investigate the collection of data in pregnancy (as a category 3 study) and a study synopsis will be submitted a post authorisation measure.	Q1 2022
The company will submit a variation within one month of identification of a viral variants with effects on safety or efficacy which may impact the benefit risk profile of sotrovimab.	
The company will submit an updated TFUQ of for 'lack of efficacy – SARS-COV2 variant information' following EMA approval- approximately one month post approval or to correspond with the nearest RMP re-submission	31 December 2021

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of licensing have been provided.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**