16 December 2021
EMA/CHMP/694191/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Xevudy

International non-proprietary name: sotrovimab

Procedure No. EMEA/H/C/005676/0000

Note

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

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List of abbreviations

$\%AUC_{exp}$	Area under the plasma concentration-time curve extrapolated from time to infinity as a percentage of total AUC
AA	amino acid
ACE	affinity capture elution
ACE2	angiotensin-converting enzyme 2
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADE	antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
AUC	area under the concentration versus time curve from time 0 to defined time t
AUC_{0-t}	Area under the serum concentration-time curve from time zero to time t
AUC0-t	Area under the plasma concentration verses time curve (from time 0 to last time point)
AUC0-X	Area under the plasma concentration verses time curve (from time 0 to X hours)
AUC_{inf}	Area under the serum concentration-time curve from time zero infinity
AUC_{last}	Area under the serum concentration-time curve from time zero to time of last measurable concentration
BLI	bio-layer interferometry
BMI	Body mass index
BP	blood pressure
C1q	complement C1q
CDC	complement-dependent cytotoxicity
CDR	complementarity-determining region
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Apparent total body clearance of the drug
C_{last}	Last measurable serum concentration
C_{max}	Maximum observed concentration
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CPE	cytopathic effect
CV	Cardiovascular
CYP	Cytochrome P450
DCO	Data cut-off
Del	Deletion
DP	Drug product
DS	drug substance
EC_{50}	Half maximal effective concentration
EC_{90}	90% effective concentration
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECMO	Extra-corporeal membrane oxygenation
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ER	Emergency room
EU	European Union
EUA	Emergency Use Authorisation
Fc	fragment crystallisable region
FDA	Food and Drug Administration
FFA	focus forming assay
FFU	focus forming units
Flu-PRO	Influenza patient-reported outcome questionnaire
Freq	Frequency
GCP	Good Clinical Practice

GH-S309	hamster chimeric version of the parental S309 that has hamster Fc regions and S309 variable regions and interacts with hamster FcRs
GISAID	Global Initiative on Sharing All Influenza Data
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
H	Human
Ha	Hamster
HEK	human embryonic kidney
HR	heart rate
hr	Hour
HRP	horseradish peroxidase
IA	Interim analysis
IC	Immunocomplexes
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgG	Immunoglobulin G
IgG1κ	immunoglobulin G1 kappa
IHC	Immunohistochemical
IL	interleukin
IP	intraperitoneal
IRR	Infusion-related reaction
ITT [Day 29]	Intent-to-treat for Day 29 analysis
IV	Intravenous
Kd	Dissociation constant
KD	equilibrium constant
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LOD	limit of detection
LS	a 2 amino acid modification of the Fc portion of the IgG1 imparting half-life extension
mAb	Monoclonal antibody
MAD	OECD Mutual Acceptance of Data
MARM	monoclonal antibody resistance mutant
MCP-1	monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MIS	Multisystem inflammatory syndrome
moDCs	monocyte-derived dendritic cells
MOI	multiple of infection
MRD	minimum required dilution
MSD	Meso-scale discovery
N, No.	number
N/A	not applicable
ND	not detected
NFAT	nuclear factor of activated T cells
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NK	natural killer
NOAEL	No-Observed-Adverse-Effect Level
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PFU	plaque forming units
PK	Pharmacokinetic(s)
PK	pharmacokinetic
PT	Preferred Term
qRT-PCR	Quantitative reverse-transcription polymerase chain reaction
RBD	receptor binding domain
RBM	Receptor-binding motif
RLU	relative light unit
SA	South Africa
SAE	Serious adverse event
SAF	Safety population
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SD	standard deviation
SDAC	Statistics Data Analysis Centre
SPR	surface plasmon resonance
T½	half-life
TCID50	median Tissue Culture Infectious Dose
TCR	tissue cross reactivity
TK	Toxicokinetic(s)
T_{last}	Time of last measurable concentration
Tmax	time at which Cmax occurred
TNF-α	tumor necrosis factor α
UAE	United Arab Emirates
ULOQ	upper limit of quantification
US	United States
Vir	Vir Biotechnology, Inc.
VIR-7831	sotrovimab, S309 monoclonal antibody with the LS modification (S309-LS)
VIR-7831-WT	a version of sotrovimab lacking the half-life extending "LS" modification in the Fc region
VIR-7832	a version of sotrovimab that contains both the LS modification (S309-LS) and an immune-modulating 'XX2" modification in Fc domain
V_{ss}	Volume of distribution at steady state
Vss	volume of distribution at steady state
VSV	vesicular stomatitis virus
V_z	Apparent volume of distribution during terminal phase
WT	wild type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services Limited submitted on 17 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Xevudy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication "Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see section 5.1)".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0468/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0468/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active Substance status

The applicant requested the active substance sotrovimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 May 2020	EMEA/H/SA/4512/1/2020/III	*Ms Rosalia Ruano Camps, Dr Karin Janssen van Doorn and Prof Brigitte Schwarzer-Daum*
17 July 2020	EMEA/H/SA/4512/1/FU/1/2020/III	*Dr Jens Reinhardt and Prof Brigitte Schwarzer-Daum*
8 January 2021	EMA/SA/0000051092	*Dr Mair Powell, Dr Jens Reinhardt and Dr Brigitte Schwarzer-Daum*

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- CMC strategy
- Preclinical data requirements to support FIH and MAA
- Conducting the FIH in outpatients with mild COVID-19 disease
- Timing of initiation of studies in different populations
- Safety monitoring and management plan in the proposed clinical studies
- Adequacy of the studies in 1) outpatients, 2) hospitalised patients, and in 3) post exposure prophylaxis setting to support approval
- Clinical development to support IM injection as an additional route of administration

Scientific advice compliance

The Applicant has received three scientific advices on quality, non-clinical and clinical aspects. Overall, the Applicant has conducted the trial in accordance with the CHMP advice, besides for the primary endpoint that was not agreed with the CHMP. Nevertheless, the Applicant continued with the non-supported primary endpoint, and included a secondary endpoint that better reflected the severity of COVID-19: development of 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.

1.6. COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

A request for rapid scientific advice was discussed by the ETF on 15 May 2020. The ETF endorsed the Scientific Advice letter and confirmed eligibility to the rolling review procedure based on the information provided by the applicant. Subsequently the ETF agreed the start of the rolling review on 9 April 2021.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP.

For the exact steps taken at ETF, please refer to section 1.7.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Blicher Co-Rapporteur: Jayne Crowe

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Liana Gross-Martirosyan

The CHMP confirmed eligibility to the centralised procedure on	25 June 2020
The ETF recommended to start the rolling review procedure on	9 April 2021
Submission of the first package via eCTD	6 May 2021
The procedure (Rolling Review 1) started on	7 May 2021
Rapporteurs' CHMP ARs and draft overviews to ETF, CHMP and EMA for consultation and comments	11 June 2021 (for CMC) and 16 June 2021 (for (non)clinical)
BWP discussion	14 June 2021
Deadline for comments	18 June 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	22 June 2021
ETF discussions on the consolidated List of Questions	24 June 2021
Start of CHMP written procedure	25 June 2021
Adoption of the 1st interim opinion for this rolling review	28 June 2021
Submission of the second package via eCTD	30 June 2021
The procedure (Rolling Review 2) started on	1 July 2021
Rapporteurs' CHMP and PRAC ARs and draft overviews to ETF, CHMP and EMA for consultation and comments	12 July 2021 (for CMC) and 16 July 2021 (for (non)clinical and RMP)
BWP discussion	15 July 2021
Deadline for comments	19 July 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	21 July 2021
ETF discussions on the consolidated List of Questions	22 July 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	22 July 2021
Adoption of the 2nd interim opinion for this rolling review	23 July 2021
Submission of the third package via eCTD	16 August 2021

The procedure (Rolling Review 3) started on	17 August
Rapporteurs' CHMP ARs on CMC and draft overviews to ETF, CHMP and EMA for consultation and comments	31 August 2021
Deadline for comments	2 September 2021
BWP discussion	06 September 202
Rapporteurs' CHMP and PRAC ARs on (non)clinical and RMP and draft overviews to ETF, CHMP and EMA for consultation and comments	13 September 2021
Deadline for comments	15 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 September 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	20 September 2021
ETF discussions on the consolidated List of Questions	21 September 2021
Adoption of the 3rd interim opinion for this rolling review	22 September 2021
Submission of the fourth package via eCTD	18 October 2021
The procedure (Rolling Review 4) started on	19 October 2021
Rapporteurs' CHMP ARs on CMC and draft overviews to ETF, CHMP and EMA for consultation and comments	27 October 2021
Deadline for comments	28 October 2021
BWP discussion	03 November 2021
Rapporteurs' CHMP and PRAC ARs on (non)clinical and RMP and draft overviews to ETF, CHMP and EMA for consultation and comments	29 October 2021
Deadline for comments	03 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	08 November 2021
ETF discussions on the consolidated List of Questions	9 November 2021
Finalisation of 4th rolling review	11 November 2021
The application was received by the EMA on	17 November 2021
The procedure started on	18 November 2021
The following GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
- GMP inspections took place at 3 sites located in China and involved in activities concerning cell banks and the manufacture and testing of the active substance. The inspections were conducted between April and	April – August 2021

August 2021 and confirmed the GMP compliance of all three sites.	
The PRAC Rapporteur's first Assessment Report was circulated to all CHMP, PRAC and ETF on	29 November 2021
The CHMP rapporteur's assessment reports were circulated to all CHMP, PRAC, BWP and ETF on	29 November 2021
The PRAC Rapporteur's updated Assessment Report was circulated to all CHMP, PRAC and ETF on	08 December 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an PRAC meeting on	08 December 2021
BWP discussions took place on	06 December 2021
ETF discussions took place on	09 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xevudy on	16 December 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	28 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally, on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to European Centre for Disease Prevention and Control (ECDC), histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 14 December 2021, there have been over 270 million confirmed cases of SARS-CoV-2 infection globally with approximately 5.31 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation and diagnosis

The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with

severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

Studies among hospitalised patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalised patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy (e.g. Veklury (EMEA/H/C/005622)), antibodies administered from convalescent plasma and hyperimmune immunoglobulins. Recently, two monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814) and Regkirona (regdanvimab, EMEA/H/C/005854) have been authorised for the treatment of COVID-19 disease in adults and, in the case of Ronapreve also adolescents (from 12 years of age and weighing at least 40 kilograms), who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

Ronapreve is also approved for prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kilograms.

Additionally, there are 4 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease, these are Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675) and COVID-19 vaccine Janssen(EMEA/H/C/005737).

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent need for vaccines and therapeutics able to prevent, mitigate and treat COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. In addition, some studies have shown that patients might experience potential sequelae, including chronic fatigue, thrombotic events post infection, non-reversible lung disease, etc; although these aspects have not been fully determined yet.

2.2. About the product

Sotrovimab is a human IgG1 mAb produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 consequently blocking cellular entry and SARS-CoV-2 infection.

The recommended dose is a single 500 mg intravenous infusion administered following dilution. It should be administered within 5 days of onset of symptoms of COVID-19.

The applicant applied for the following indication: "Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see section 5.1)."

2.3. Quality aspects

Note to reader:

Exemptions from Article 51 of Directive 2001/83/EC regarding testing of the finished product at the non-EU site were sought for all quality control tests. Finished product release testing will be performed at the non-EU site until 31st March 2022. From this date onwards, finished product release testing will be performed by a site located in the EU (GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana, 90, 43056 San Polo di Torrile, Parma, Italy). Having considered the ongoing COVID-19 epidemiological situation, the duration of the derogations and that it is acceptable from a quality point of view, this approach was accepted and reflected accordingly in the terms of the Marketing Authorisation (Annex II.A of the Product Information).

The Applicant also informed that they intend to have a period of transition between the Article 5(3) of Regulation No 726/2004 and product supplied under the terms of the Marketing Authorisation in order to avoid disruption of the market. Whilst noting that these transition arrangements are in the remit of Member States, the CHMP noted that there is no significant difference in terms of quality, as all batches tested for supply in the European Union (EU) meet the tightened specifications presented in the Marketing Authorisation.

The below quality overview reflects the data submitted in Module 3 during the rolling review procedure and Marketing Authorisation application.

Introduction

Xevudy finished product (FP) is presented as a concentrate for solution for infusion supplied in a single-use vial containing 500 mg of sotrovimab as active substance (AS) in 8 mL (62.5 mg/mL).

Other ingredients are histidine/ histidine monohydrochloride buffer, sucrose, polysorbate 80, methionine, and water for injections.

The product is available in vials with a fill volume of 8.6 mL to allow for a delivery of 8 mL.

2.3.1. Active Substance

General Information

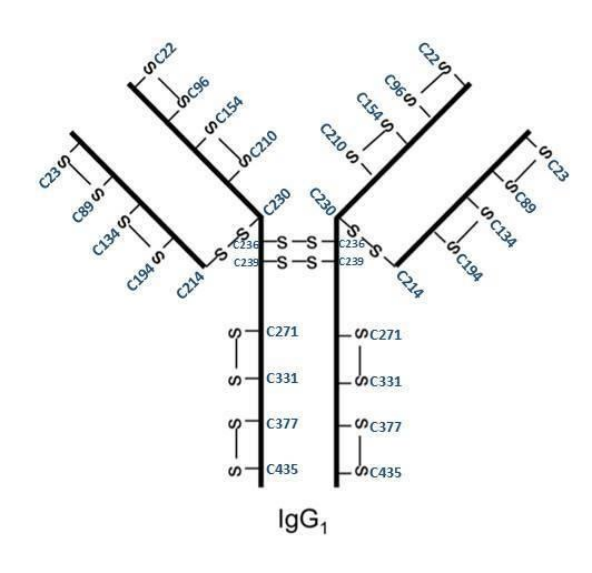
The active substance of Xevudy is sotrovimab (INN) (also known as VIR-7831 or GSK4182136).

Sotrovimab is an engineered human immunoglobulin G (IgG1) monoclonal antibody (mAb) that binds to a highly conserved epitope on the spike protein receptor-binding domain. The epitope has minimal overlap with the binding site of the angiotensin-converting enzyme 2 (ACE2) receptor on the receptor-binding part of the spike protein (RBD), and the mAb does not compete with ACE2 for RBD binding (assayed on immobilised ACE2 by biolayer inferometry, using full-length and Fab formats). Nevertheless, sotrovimab neutralises SARS-CoV-2 *in vitro*, and thus inhibits viral replication.

Sotrovimab is also able to engage in Fc-mediated receptor activities (FcγRIa, FcγRIIa and FcγRIIIa). The sotrovimab Fc has been engineered to provide an extended half-life through inclusion of the LS mutations, which enhance FcRn binding.

Sotrovimab is produced in Chinese hamster ovary (CHO) cells and consists of 2 heavy chains (HC) and 2 light chains (LC) with 2 LC and 4 HC interchain and 4 intrachain disulfide bonds, as presented in Figure **1**.

Figure 11: Disulfide bond map



Each heavy chain contains a single N-linked glycosylation site at Asparagine 307.

The amino acid sequence of the heavy and light chain sequences of sotrovimab are shown in Figure **2**.

The molecular formula of non-glycosylated sotrovimab with the C-terminal lysine truncation and N-terminal pyroglutamate conversion on heavy changes and intact disulfide bonds is $C_{6480}H_{10030}N_{1738}O_{2036}S_{40}$. The theoretical molecular mass of this form is 146 142 Da.

Figure 22: Amino acid sequence of sotrovimab

Heavy Chain Amino Acid Sequence

```
  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 PREEQY[N]STY 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

```
  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
```

Manufacture, process controls and characterisation

GMP

The active substance is manufactured at WuXi Biologics Co., Ltd., 108 Meilang Road, Binhu District, WuXi Jiangsu, China; a site confirmed to be GMP compliant by the EU supervisory authority.

All other sites involved in the active substance manufacturing and controls are also confirmed to be GMP compliant.

Description of manufacturing process and process controls

An active substance batch consists of the harvest from production bioreactors, which are inoculated from a seed culture derived from a single master cell bank (MCB) vial thaw.

The manufacturing process intended for commercial production, is overall standard for monoclonal antibodies using a suspension-adapted CHO cell line. In the inoculum expansion stages of the upstream process, cells from a single MCB vial are progressively expanded in cell culture medium, until a sufficient quantity of viable cells have been produced to meet the required inoculum density within the bioreactor. In order to provide flexibility in the production schedule (i.e. timing of the production bioreactor inoculation), the inoculation expansion process was designed to allow repeat passaging of cells through additional seed train passages within the bioreactor.

The downstream process consists of protein A chromatography, low pH viral inactivation, depth filtration, anion-exchange chromatography (AEX) chromatography, viral filtration, ultrafiltration/diafiltration (UF/DF), formulation, filtration into the active substance storage container and freezing.

The active substance formulation contains sotrovimab in a L-histidine/L-histidine monohydrochloride buffer containing L-methionine, sucrose, and polysorbate 80 at a pH of approximately 6. The sotrovimab active substance is stored and shipped frozen.

The upstream and downstream manufacturing processes have been sufficiently described and flow diagrams have been provided.

Process parameters and performance attributes together with their acceptable ranges, and in-process pool hold times and storage conditions are further described below under critical quality attributes (CQAs), control strategy and process characterization.

Control of materials

Overviews of the raw materials used in the sotrovimab active substance upstream and downstream manufacturing process have been provided, including their pharmacopoeial standards and corresponding usage in the process. The excipients used to formulate the active substance and finished product are tested according to the Ph. Eur.

Overviews of the resins, membranes, depth filters and storage flask and bags used in the active substance manufacturing process operations have been also sufficiently described.

Except for the HCl and NaOH used for pH adjustment, the raw materials of non-compendial grade are as a minimum controlled for endotoxin in line with the raw material specifications. The resins are controlled for bioburden. The controls used 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. Serum was used in preparation of the host cell bank prior to adaptation to a serum-free process, which is supported by a TSE risk assessment. To generate the cell substrate, the CHO- host cell line was transfected with expression plasmids containing the antibody heavy and light transgenes in separate plasmids, and co-transfected with a helper plasmid containing a transposase to aid integration. The transposase expression is transient as the plasmid does not contain a selection marker and hence is lost during continued cultivation. The transfected cells were selected using antibiotics to produce a stable pool, which was used in the Gen1 manufacturing process. A single cell clone derived from the stable pool used for the Gen1 manufacturing process was used for the preparation of a MCB for the Gen2 manufacturing process.

The studies to assess the safety, identity and genetic stability for the MCB and end of production cell bank (EoPCB) are based on the requirements of ICHQ5A, Q5B and Q5D. Characterisation testing established the absence of infectious agents.

The suitability of analytical methods used during viral validation has been demonstrated. The MCB and EOPCB have been sufficiently characterised.

Control of critical steps and intermediates

Summary tables have been provided which outline the critical process parameters (CPPs) and critical performance attributes (CPAs) as well as their acceptance ranges.

There are no process intermediates defined, only in-process pools. This is acceptable.

Process validation and evaluation

A three-stage approach has been applied to the active substance process validation. Process validation was initiated by small-scale studies and characterisation studies (stage 1) followed by process performance qualification (PPQ) (stage 2) and ongoing process verification (stage 3).

Overall, the results of the supporting PPQ validation studies confirm that the parameters investigated were properly validated and contributed to high purity and quality of sotrovimab active substance.

The process validation is considered successful based on data from the three PPQ batches.

Manufacturing process development – history and comparability

Three process versions have been utilised: Gen1 and Gen2 clinical and Gen2 commercial active substance process. The major changes through the process development were a change from a non-clonal stable cell pool to an MCB, scale up and site transfer.

Gen1 to Gen2 clinical process comparability: The degree of comparability of active substance manufactured by the Gen1 and the Gen2 processes was evaluated by comparing results from in-process testing active substance release, extended characterisation and active substance stability.

In conclusion, the process performance and the product quality are considered sufficiently comparable between Gen1 and Gen2.

Gen2 clinical to Gen2 commercial process changes: The Gen2 clinical process was designed for site transfer to the active substance manufacturing site and a change in scale to fit, the commercial process is referred to as Gen2 commercial. The changes are sufficiently explained with the only major changes being the mentioned site transfer and change in scale to fit the commercial process. The upstream unit operations are overall the same between the two Gen2 scales, with one additional seed expansion phase in the Gen2 commercial process. The downstream unit operations and sequence are identical between the two Gen2 scales, with minor changes in purification equipment size, associated controls and a change in active substance container for storage.

Gen2 clinical to Gen2 commercial comparability: The process performance and impurity clearance of Gen2 commercial is considered comparable with Gen2.

In conclusion, the changes introduced between the three process versions are sufficiently described and the comparability of material from the three process is considered sufficiently demonstrated.

CQAs, control strategy and process characterisation

The design of the control strategy is based on quality by design (QbD) principles. No design space is claimed.

The assigned CQAs and non-CQAs are found appropriate. Based on the identified CQAs, a failure mode effect analysis (FMEA) risk assessment was performed to select process parameters and raw materials for process characterisation (PC) studies. Appropriate process parameters (PPs) were evaluated during the process characterisation, as supported by the FMEA provided.

The small-scale models selected for the PC studies to represent the manufacturing scale are satisfactory justified and/or qualified by largely comparable process performance and product quality results.

PC studies were performed to evaluate the effect of high-risk parameters and raw materials on the CQAs and process performance, and subsequently determine their preliminary criticality. The established acceptable ranges (PARs) are considered sufficiently justified by the PC and virus clearance study data.

The proposed in-process pool and buffer hold times and storage conditions are supported by the provided biochemical stability data. The resin lifetime studies support an acceptable number of re-use cycles for the AC resin and AEX resin. Ultrafiltration membranes are also intended to be re-used, and concurrent evaluation for membrane lifetime is performed and monitored through formal lifetime protocols. The assessment of the potential extractable and leachable components of the sotrovimab active substance manufacturing process support a negligible risk.

Characterisation

One sotrovimab active substance batch, manufactured according to the commercial Gen2 process, was used to fully characterise the sotrovimab molecule. Primary and higher order structures, post-translational modifications, glycosylation profile, charge variants, purity, thermal stability, and biological attributes have been characterised using state of the art methods. Head-to-head characterisation data from clinical Gen1, Gen2 and commercial scale Gen2 active substance batches were evaluated in comparability studies and comparability has been established.

The majority of sotrovimab protein contained N-terminal pyro-glutamic acid (PyrGlu) and lacked C-terminal lysine (Lys), which is standard for IgG molecules.

The biological and binding properties of sotrovimab with the SARS-CoV-2 spike protein RBD, have been characterised using various analytical methods.

Degradation studies were conducted to analyse the potency and FcRn binding of degradations products. Sotrovimab samples were stressed by different methods. Overall, potency and FcRn binding was not significantly affected by relatively large changes in charge variants, isomerization, deamidation, oxidation, level of non-covalently bound HMW species, and level of fragments.

In conclusion, sotrovimab has been adequately characterised.

Impurities

Product-related impurities are molecular variants of sotrovimab that may arise during manufacturing or storage and that do not have properties comparable to those of the desired product with respect to activity, efficacy and safety. Based on the comprehensive characterization of sotrovimab active substance molecular variants were identified and classified as either product-related substances if their potency and safety was deemed to be comparable to those of sotrovimab, or product-related impurities. The risk assessment carried out to determine whether variants were product-related substances or impurities has been presented.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications and justifications of specifications

Active substance specification covering relevant parameters has been provided. The specification for release and stability of sotrovimab active substance have been set in accordance with ICH Q6B and includes suitable physiochemical tests and appropriate tests for identity purity and potency to control relevant characteristics of monoclonal antibodies.

The panel of analytical methods used for release and stability control of sotrovimab active substance are in general considered broad and relevant for the control of a mAb.

Specification limits were based on a combination of published limits, clinical experience, batch / stability data and are acceptable.

The Applicant is recommended to re-evaluate the specification limits and to provide a revised Justification of Specification when a minimum number of active substance batches and finished product batches at the commercial scale have been completed or no later than 2 years after the of approval of the marketing application (Recommendation).

Analytical methods and Validation of analytical methods

The panel of methods used to guarantee the quality of the active substance are in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The methods are generally considered suitable for their intended use; however, the Applicant is recommended to further characterise the generic HCP method to show antibody coverage of those HCPs that persist through the purification process (Recommendation).

The compendial analytical procedures are performed in accordance with the methods described in the relevant pharmacopoeia. Bioburden and endotoxin test methods were adequately qualified for use with the active substance demonstrating recovery of challenge organisms in the presence of product.

The non-compendial analytical procedures have been described in sufficient details. System suitability criteria, assay and sample acceptance criteria are specified where relevant and the acceptance criteria have been confirmed during the validation of the methods.

The Applicant has provided validation overviews for the non-compendial methods. The non-compendial analytical methods have been appropriately validated according to ICH Q2 to control active substance and finished product, at the relevant active substance testing site and/or finished product testing site except for the potency assay. This assay is both applied in active substance and finished product release control, and has been sufficiently validated at the active substance testing site outside the EU, but transfer to the EU finished product testing site is delayed and will be finalised during the early part of 2022, which is acceptable. Finished product release testing will be temporarily performed at the non-EU site until 31st March 2022. From this date onwards, finished product release testing will be performed by a site located in the EU (GSK Parma, Italy). Annex II.A of the Product Information reflects this temporary exemption. The method transfer results are announced to be available in Q1 2022 and a summary of the results, along with a method transfer validation protocol with pre-defined acceptance criteria, should be provided (Recommendation).

The system suitability criteria are in general found adequate to confirm that the methods are in control during routine testing. However, the Applicant is recommended to provide the requested additional validation work regarding the quantification limit of impurities by the SE-HPLC and r/nr-CE-SDS reduced (Recommendation).

Batch analysis data

At the time of CHMP Opinion, several Gen/Gen2 clinical batches, and several Gen 2 commercial batches have been manufactured. All results are within the active substance specification valid at the time of testing, and for parameters tested throughout development all results are also within the current specification, except for the change in protein concentration. Except for also a slight variation in charge variants within Gen2 commercial batches, batch-to-batch consistency has been confirmed.

Reference standard

The primary reference standard (PRS) and the first working reference standard (WRS) were sourced from the same commercial scale active substance batch. The clinical reference material (CRM) and PRS/WRS were sourced from active substance material with a different concentration of sotrovimab and with a slightly different level of sucrose, however, these differences are not considered to affect comparability between reference standards.

The initial reference material (clinical reference material (CRM)) was evaluated during the Article 5(3) procedure for Xevudy and was found adequately qualified and suitable for its intended use. The active substance parent batch from which PRS and current WRS was prepared met all active substance release testing acceptance criteria, and extended characterization confirmed that the PRS and the current WRS were comparable to the previous reference standard. The PRS and current WRS are

adequately characterised and qualified and are suitable for their intended use as both active substance and finished product reference material.

The reference standards are stored at -70°C. The PRS/WRS stability testing protocol is acceptable.

Future WRS lots will be qualified against the PRS, and a qualification protocol has been provided.

Container closure

Sotrovimab active substance is stored in sterile single-use bags. The container closure has been tested by the vendor. An extractable/leachable study has been provided.

Stability studies support that the container closure protects the active substance from loss of water and gas transmission and shows overall compatibility between the container closure system and the active substance.

The container closure specification is acceptable.

Stability

A shelf life of 12 months is proposed for sotrovimab active substance when stored under long-term storage conditions of ≤ -35°C.

Data from primary stability studies and supporting stability studies are available. Stability test results meet the commercial acceptance criteria at long-term storage conditions for all primary and supporting stability lots. The active substance stability studies have been performed in accordance with ICH Q5C and Q1A(R2).

The analytical methods applied are considered appropriate as stability indicating methods, and the stability protocols are acceptable. The containers used for the stability studies are considered representative of the container closure system used for long-term storage of the active substance.

Based on the provided stability data and extrapolation study, the demonstrated comparability between active substance Gen2 commercial and previous generations, and since monoclonal antibodies of the IgG1 isotype are generally accepted to be highly stable molecules; the claimed shelf life of 12 months is considered acceptable. The Applicant is recommended to provide updated available stability data at long-term conditions (Recommendation).

2.3.2. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Sotrovimab finished product is presented as a concentrate for solution for infusion supplied in a single-use vial containing 500 mg of sotrovimab as active substance (AS) in 8 mL (62.5 mg/mL). Other ingredients are histidine/ histidine monohydrochloride buffer, sucrose, polysorbate 80, methionine, and water for injections. All excipients used in sotrovimab finished product are of compendial grade.

The qualitative and quantitative composition for the labelled volume of 8 mL of sotrovimab 62.5 mg/mL finished product, as well as the function and quality standard of each component, have been provided.

There are no overages in the sotrovimab finished product.

Formulation development and robustness

Formulation development was conducted to establish a finished product formulation with the desired quality target product profile (QTPP) of sotrovimab. A Quality Target Product Profile (QTPP), as

described by the ICH Guideline Q8 (R2): Pharmaceutical Development and Q9: Quality Risk Management, was defined to ensure that the safety and efficacy of sotrovimab could be maintained as described in the Target Product Profile (TPP). The QTPP for the finished product was refined over time and was used to guide the product development effort to satisfy clinical and commercial requirements.

A concentration of 62.5 mg/mL of sotrovimab in L-histidine/L-histidine-hydrochloride, L-methionine, sucrose, PS80 with a pH of approximately 6 was chosen as the final Gen2 formulation. Comparability between Gen1 and Gen2 formulation has been established.

Results from an active substance and finished product robustness study confirmed the robustness of the proposed sotrovimab formulation for reasonable variations in composition and pH and supported the appropriateness of the formulation and excipients selected.

Manufacturing process development – history and comparability

The formulation and process for the commercial sotrovimab finished product presentation (Gen2) is comparable to that of the early clinical presentations.

Sufficient data has been provided to justify that comparability was achieved between early process and commercial process

Process characterisation and control strategy

The critical quality attributes (CQA) identified for the sotrovimab finished product have been presented and discussed. The CQAs are controlled by the critical process parameters and performance attributes in the finished product manufacturing process. The established control strategy of the commercial manufacturing process is considered acceptable.

Product-contact material compatibility and photosensitivity

A summary of studies supporting the commercial process has been provided.

Compatibility and in-use stability

Sotrovimab is administered in IV bags containing either normal saline (0.9% Sodium chloride (NS)) or dextrose (5% Dextrose in water (D5W)). Compatibility studies were conducted in IV bag materials and with tubing, syringe, needle and in-line filter made of standard material used in hospitals. Diluted finished product was stored in the administration sets and evaluated for biochemical stability.

Microbial hold studies were conducted, and results showed that no meaningful significant increase in any of the challenge organisms was detected using Gen 2 material in the microbial challenge study.

Overall, the compatibility study confirm that finished product is compatible with the material tested and with NS and D5W.

Manufacture of the product and process controls

GMP

The sotrovimab finished product is manufactured, packaged and batch released at an EU site supported by a valid proof of GMP compliance.

Collectively, GMP compliance is considered suitably documented for sotrovimab finished product, and a QP declaration has been provided.

Description of manufacturing process and process controls

The sotrovimab finished product manufacturing process is standard and consists of active substance thawing at room temperature, pooling, diluting to target protein concentration, mixing, bioburden reduction filtration, sterile filtration, filling, stoppering and capping.

All processing steps are performed at room temperature. Once labelling and packaging are completed, the sotrovimab finished product is stored and shipped at 2 – 8 °C protected from light. No reprocessing is proposed.

Overall, the manufacturing process, the equipment used, and the measures to ensure a sterile product are considered adequately described.

Process validation and/or evaluation:

Three consecutive PPQ batches were manufactured according to pre-approved protocols at the intended commercial manufacturing site according to the proposed commercial finished product manufacturing process and covering the proposed commercial batch size range. All process steps were validated.

Final release testing and in-process results for the three PPQ batches all met the acceptance criteria. In addition, the process validation data for all individual process steps comply with the pre-defined acceptance criteria.

The proposed process parameter and in-process control targets and limits for the finished product manufacturing process, are considered justified by the process validation.

Filter validation studies have been performed as expected. Sterility assurance included validation of sterilization of vials and stoppers and media fills.

Process times / hold times have overall been validated.

Overall, the process validation demonstrate that the process performs consistently, and the proposed commercial process is considered supported.

Shipping qualification has been performed and all quality attributes tested met the acceptance criteria.

Product specification, analytical procedures, batch analysis

Specification and justification of specifications

Finished product specification covering relevant parameters, has been provided. The specification for release and stability of sotrovimab finished product have been set in accordance with ICH Q6B and covers relevant characteristics: appearance, content, identity, purity, potency and general compendial tests.
The panel of analytical methods used for release and stability control of sotrovimab finished product are considered broad and relevant for the control of a mAb.

Finished product release and stability specification acceptance criteria for some physiochemical tests, identity, and potency are the same as those applied to active substance release and stability.

Release and stability specification limits for visible and sub-visible particles and for sterility are set in accordance with the relevant Ph. Eur. monographs. Finished product container closure integrity testing should pass the USP method.

All compendial methods and acceptance criteria are acceptable.

As for active substance specifications, many finished product specification acceptance criteria were determined by statistical analysis.

The Applicant is recommended to re-evaluate the specification limits and to provide a revised Justification of Specification when a minimum number of active substance batches and finished product batches at the commercial scale have been completed or no later than 2 years after granting of the marketing authorisation application (Recommendation).

Analytical methods, acceptance criteria and validation of analytical methods

Many analytical methods used for release and stability testing of sotrovimab finished product are equal to those used for the active substance or are compendial. Methods for polysorbate 80, sterility, extractable volume, visible particles, sub-visible particles, osmolality and extractable volume are only used for the finished product.

The compendial methods for testing endotoxin and sterility have been verified using sotrovimab finished product to show that the sample material itself does not inhibit the assays.

The container closure integrity test (CCIT) method is based on guidance from USP <1207> and is performed on stability batches only which is acceptable.

Batch analysis data

At the CHMP Opinion stage, several batches from the early phase and commercial phase process have been manufactured. All results are within the finished product specification valid at the time of testing, and for the parameters tested throughout development all results are also within the current specification, except for the change in protein concentration. There is good batch-to-batch consistency between the commercial Gen2 (EU) batches.

Reference standard

The same reference standard used for active substance analyses also applies to relevant analyses of the finished product. Please refer to the description of the reference standard in the active substance part.

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.

A summary of the risk assessment for elemental impurities in line with ICH Q3D has been included. It can be concluded that the risk and the impact on patient safety associated with the presence of elemental impurities is negligible.

A risk evaluation concerning the possible presence of nitrosamine impurities in the finished product has been performed considering all suspected root causes. Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or finished product. Therefore, no additional control measures are deemed necessary.

Stability of the product

A shelf-life of 18 months is claimed for sotrovimab finished product when stored under long-term storage conditions of 5 ± 3°C.

Data from primary stability studies and supporting stability studies are available. Stability test results meet the commercial acceptance criteria at long-term storage conditions for all primary and supporting stability lots. The finished product stability studies have been performed in accordance with ICH Q5C and Q1A(R2).

The analytical methods applied are considered appropriate as stability indicating methods, and the stability protocols are acceptable. The containers used for the stability studies are considered representative of the container closure system used for long-term storage of the finished product.

Based on the stability data provided, the comparability demonstrated throughout process development, the justifications provided from extrapolations of the accelerated stability data, and since monoclonal antibodies of the IgG1 isotype are generally accepted to be highly stable molecules, the claimed shelf-life of 18 months is considered acceptable. The Applicant is recommended to provide updated available stability data at long-term conditions when the data is available (Recommendation).

A photostability study in line with ICH Q1B to evaluate the light sensitivity of sotrovimab finished product has been provided. Light-exposed samples demonstrate a significant degradation supporting the 'protect from light' claim in the summary of product characteristics (SmPC). Sample stored in foil-lined carton, simulating the secondary packaging, was not affected by the light exposure confirming the suitability of the secondary container closure.

The diluted solution 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.

Post approval change management protocol(s)

A post approval change management protocol (PACMP) has been included regarding a new working cell bank and alternative active substance manufacturing site.

Adventitious agents

Non-viral agents

No TSE-risk materials have been identified. Compliance with TSE-Guideline EMEA 410/01 rev03 has been demonstrated.

Viral agents

The MCB and EOPCB were tested and confirmed safe with regards to viral adventitious agents in accordance with ICH Q5A.

Virus clearance capacity of the manufacturing process

The capability of the commercial sotrovimab process to remove or inactivate viruses has been evaluated with the worst-case conditions employed for relevant steps and is considered acceptable.

2.3.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The quality data provided in Module 3 are considered adequate and sufficient to support a well-controlled manufacturing process and a high quality of sotrovimab.

The outstanding issues have been satisfactory resolved during the rolling review phases, however some data is still pending and will be submitted post-authorisation as agreed by the CHMP. These especially concern documentation of the method transfer of the potency assay to the EU finished product testing site which is ongoing (Recommendation), and additional validation of some purity methods (Recommendation). Other CHMP endorsed post-authorisation measures include submission of active substance and finished product real-time stability data at long-term conditions covering all of the approved shelf life once available (Recommendation), and re-evaluation of the active substance and finished product release and stability specifications following further manufacturing experience or no later than 2 years after the approval of the marketing application (Recommendation). The Applicant is also recommended to further characterise the HCP method (Recommendation). In light of the on-going COVID-19 pandemic the submission of these data post-authorisation is acceptable and does not, from a quality point of view, preclude the granting of the marketing authorisation.

Lastly the Applicant should inform the authorities when the transfer of finished product release testing to EU site has been conducted (due date 31.03.2022). From this date onwards, finished product release testing will be performed at the EU site. Annex II.A of the Product Information reflects this temporary exemption.

A PACMP has been submitted and accepted for the introduction of a new active substance manufacturing site, including implementation of a WCB.

2.3.4. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Xevudy is considered acceptable when used in accordance with the conditions as defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated.

The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

2.3.5. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Applicant is recommended to re-evaluate the active substance and finished product specification limits and to provide a revised justification of specification.

2. The Applicant is recommended to further characterise the generic HCP method to show antibody coverage of those HCPs that persist through the purification process.

3. Additional validation data to support the purity methods.

4. The Applicant is recommended to provide real-time active substance and finished product stability

data at long-term conditions to cover the claimed shelf life.

5. The Applicant is recommended to submit the transfer validation protocol and a summary of the analytical method transfer test results to an EU site for the potency assay.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

Sotrovimab (also known as VIR-7831, GSK4182136) is a human immunoglobulin G1 kappa (IgG1κ) SARS-CoV-2 neutralizing monoclonal antibody (mAb) derived from the parental mAb S309, a mAb directed against the spike protein of SARS-CoV-2 [Pinto 2020]. The amino acid sequence of the complementarity-determining regions (CDR) of sotrovimab is identical to the parent molecule S309, except for one amino acid modification (N55Q) introduced to aid antibody developability. The Fc domain of sotrovimab includes the 2 amino acid "LS" modification that extends antibody half-life.

Sotrovimab is derived from the parental mAb S309, which was originally identified from a SARS-CoV-1 infected survivor. The proposed mechanism of action is through its ability to target the spike protein of SARS-CoV-2; sotrovimab will suppress viremia and accelerate clearance of infected cells.

2.4.2.1. Primary pharmacodynamic studies

The primary pharmacology of sotrovimab was studied following in vitro binding assays to SARS-CoV-2 spike protein monomer and trimer, in vitro neutralization of SARS-CoV-2 live virus and pseudotyped virus, and epitope mapping and conservation analyses. In addition, in vitro resistance selection studies exploring the barrier to resistance and generation of variants conferring reduced susceptibility as well as characterization of sotrovimab effector functions were conducted. In vivo anti-viral activity was evaluated in a Syrian golden hamster model of SARS-CoV-2 infection.

In vitro primary pharmacodynamic studies

A series of in vitro studies have been performed to assess the binding of sotrovimab to the spike protein (report 2020N456937). An equilibrium constant (KD) of 0.21 nM was measured by surface plasmon resonance to a recombinant RBD domain of the spike protein. A half maximal effective concentration (EC50) value of 20.40 ng/mL calculated using an enzyme-linked immunosorbent assay (ELISA) to the spike monomer protein. In addition, flow cytometry detected binding of sotrovimab to cell surface-expressed SARS-CoV-2 spike protein trimer.

A series of in vitro studies have been performed to assess the antiviral activity. Concentration-dependent viral neutralisation was observed, with an average EC50 value of 100.1 ng/mL against the SARS-CoV-2 isolate USAWA1/2020 in VeroE6 cells (report 2020N457420). For the majority of other studies, a VSV-based luciferase reporter pseudotyped virus system is utilised to determine neutralisation activity (report 2020N456924). Using this approach an EC50 of 24.06 ng/mL for sotrovimab was calculated, although it is observed that in subsequent studies there is some variance in the EC50 values calculated for the wild type virus, which likely reflects the biological variance between experiments. Based on the pseudotyped virus neutralisation data provided (report 2021N470273), it is expected that sotrovimab will maintain its activity against SARS-CoV-2 variants of concerns including the alfa (B.1.1.7), beta (B.1.351), gamma (P.1) and Epsilon (B.1.427/B.1.429) variants, sotrovimab

retained activity against pseudotyped virus expressing the B.1.1.7, B.1.351, P.1 or B.1.427/B.1.429 spike variants. Fold-changes in EC50 ranged from 0.35- to 2.30-fold. The reported EC50 of sotrovimab against the omicron (B.1.1.529) pseudotype was 336.4 ng/mL (2021N495027), representing a 2.7-fold reduction in neutralising activity, compared to the Wuhan spike pseudotype.

Activity of sotrovimab was also assessed against SARS-CoV-2 live virus using the alfa (B.1.1.7), beta (B.1.351) and gamma (P.1) variants (report 2021N475485). No significant shift in the EC50 or EC90 values were seen for the beta (B.1.351) and gamma (P.1) variants, however, a shift was seen for the alfa variant of 3-fold and 4.1-fold for the EC50 and EC90 activity values respectively. As part of the same study report an in vivo study in hamsters is reported to have demonstrated that based on weight loss measurements sotrovimab at 5 mg/kg and 30 mg/kg was seen to protect B.1.1.7-infected hamsters. However, insufficient detail and information is provided in relation to this study to be able to conclude on any such protection and its potential relevance (see further discussion below). The activity of sotrovimab has also been tested against emerging spike variants including the B.1.617 lineage (report 2021N475740), including data on activity against the sub lineage Delta B.1.617.2. Sotrovimab neutralised the B.1.617.1 and B.1.617.2 variants with geometric means EC50 of 118.64 ng/ml and 51.29 ng/ml, respectively (0.9- and 0.4-fold change vs. wild type, respectively) and geometric mean EC90 of 379.89 ng/ml and 219.08 ng/ml, respectively (1.0-fold and 0.6-fold changes vs. wild type, respectively).

The epitope on the SARS-CoV-2 spike protein to which sotrovimab binds has been mapped using crystallography (report 2020N456987; epitope conservation and activity against pseudotyped virus encoding epitope variants in reports: 2021N470274, updates 2021N471870, 2021N476139, 2021N477635 and 2021N481341). The identified 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. An analysis of the GISAID database suggested that the amino acids in the epitope were highly conserved with ≥99.97% conservation amongst the available sequences. To evaluate the epitope variant susceptibility to sotrovimab, amino acid substitutions were introduced into the SARS-CoV-2 spike coding sequence and assessed in the pseudotyped virus neutralization assay. Variants at two positions resulted in significant EC50 shifts indicating reduced susceptibility to sotrovimab, E340 (>297 fold) and P337 (180-fold). Not all residues in the identified epitope, and for which variants were noted, were tested for possible differences in binding by sotrovimab. The shift in potency was not only dependent on the particular residue but in addition, the amino acid change at that position as exemplified by P337. Therefore, whilst there are data supporting that some residues of the epitope may not be critical in determining sotrovimab binding, this should be interpreted with caution, as it may be dependent on the amino acid substitution involved.

An assessment of the resistance barrier was performed in vitro using a related antibody, VIR-7832, which contains a "XX2" modification in the Fc domain but with identical Fab regions (report 2020N456627). 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 performed where 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 identified amino acid substitutions E340A, R682W, and V1128F which were detected in <0.002% of sequences in the GISAID database and were tested in the pseudoviral system for neutralisation activity by sotrovimab. No effect was seen for variants R682W and V1128F, however, E340A had a >100-fold increase in EC50 value and thus is identified as being a monoclonal antibody resistance mutations (MARM) for sotrovimab.

An assessment of Fc effector function (report 2020N456792) 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 pharmacodynamic studies

A total of three different in vivo studies have been performed in the Syrian Golden Hamster model of SARS-CoV-2 infection to assess the nonclinical efficacy of sotrovimab. In report 2020N457284, both Day -1 prior to infection and Day -2 prior to infection (prophylactic) paradigms of treatment were assessed. In both instances VIR-7831-WT, an antibody which only differs from sotrovimab in that it lacks the "LS" mutation, 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. Report 2021N471868 utilised GH-S309, a modified version of the parental antibody S309 containing a hamster IgG2a Fc region. This study was performed since it was suggested that Fc effector function for a human IgG1 like sotrovimab may be diminished in hamsters. However, of note an assessment of immunocomplexes (IC) formed by sotrovimab or GH-S309 to hamster splenocytes provided some evidence that limited Fc effector function is evident for sotrovimab in hamsters. The study was only performed using the prophylactic model of antibody dosing 2 days prior to infection. Decreases in viral load, infectious virus titers and improvement in lung pathology were seen in the study with 4 mg/kg of GH-S309. The final in vivo study (report 2021N471990) used the actual candidate antibody, sotrovimab. Here only the prophylactic setting was assessed where beneficial effects were seen in terms of total and infectious viral loads at doses $\geq$ 5 mg/kg. Furthermore, using weight loss as a surrogate for disease burden significant differences were seen in weight as assessed on Day 4 post infection for doses of 5 mg/kg and 15 mg/kg. It is notable that at Days 1-3 there is no apparent differences in weight and only at Day 4 is there a divergent in the graphs. Changes in lung pathology were only reported 2021N471868. However, both2020N457284 and 2021N471990 report that the lungs were collected for necropsy. The Applicant has indicated that pathological examination of the lung tissues was not performed, though data on lung weight are available. These demonstrate that compared to infected controls, the lung weight in VIR-7831-WT and sotrovimab treated animals at doses $\geq$ 0.5 mg/kg was decreased, suggesting decreased lung inflammation. Although limited, this does provide some additional indication of a functional effect of sotrovimab treatment on lung pathophysiological changes associated with SARS-CoV-2 infection.

In addition, a preliminary summary of an in vivo study in hamsters challenged with the UK (B.1.1.7) SARS-CoV-2 variant is provided in report 2021N475485. In this study sotrovimab appears to maintain efficacy in vivo against this variant. In this study, the MAH disclosed that sotrovimab was administered 24 hours prior to infection. While the full data from this study (including total lung viral load and lung TCID50) are not yet available, these data in report format will be made available once finalised.

Taken together the studies provided some limited evidence that sotrovimab is effective in a relevant model of SARS-CoV-2 infection. There are limitations with the in vivo studies as in all models used the antibody was dosed prior to intra-nasal infection. In the current application the proposed indication is for the treatment of COVID-19 patients. The Applicant has suggested that the intra-peritoneal dosing of the antibody on Day -1 prior to infection is reflective of a treatment paradigm based on Cmax levels not being achieved until 24-36 h post dosing. Whilst there may be some limited basis for this argumentation exposure to the antibody will have occurred prior to infection, albeit if not at maximum levels. Ultimately, the clinical data will be decisive in determining whether the product is efficacious or not.

2.4.2.2. Secondary pharmacodynamic studies

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 were performed using cells which express that express FcγRs: monocyte-derived dendritic cells (moDCs), peripheral blood mononuclear cell (PBMCs) and U937 macrophage cells, thus allowing assessment of Fc-dependent mechanisms of ADE of infection (2020N456687). No differences in viral entry or replication were seen in these cells in the presence of sub-therapeutic levels of sotrovimab. In addition, similarly in permissive VeroE6 cells no differences were seen suggesting that no effect on FcR independent mechanism by sotrovimab. Furthermore, levels of cytokines and chemokines were measured in the presence of sotrovimab in the aforementioned cell lines with no increases seen in the presence of sotrovimab. In addition, all of 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.

2.4.2.3. Safety pharmacology programme

Safety pharmacology core battery endpoints were included in the repeat-dose study in cynomolgus monkeys, as described in the ICH S6 (R1) guideline. 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).

2.4.2.4. Pharmacodynamic drug interactions

In vitro studies examining any drug interactions with remdesivir or bamlanivimab were performed (reports 2020N456694 and 2021N466415 respectively). It was demonstrated that no interference between the products was observed. A pharmacodynamic interaction study was performed to assess whether sotrovimab interferes with other COVID-19 treatments. In these in vitro studies, sotrovimab was studied in combination with the antiviral, remdesivir, or another monoclonal antibody targeting a different epitope on the spike protein of SARS-CoV-2, bamlanivimab. In these studies, a SARS-CoV-2 nano luciferase reporter virus encoding nano luciferase in place of the viral ORF7 was utilised. No antagonism was observed, and the combination of sotrovimab resulted in additive effects in both settings. Considering the mechanism of action of remdesivir differs from that of monoclonal antibodies like sotrovimab a PD drug interaction would not be expected. Although bamlanivimab as a monoclonal antibody against the spike protein could have PD drug interaction potential, the epitope differs from that of sotrovimab, which is seen in the lack of antagonism in the studies performed.

An in vitro study performed in live virus assays and pseudotyped virus assays showed that sotrovimab alone or in combination with bamlanivimab maintained activity against the tested variants (2021N477024). The tested variants 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).

It was shown that the utilising combination of sotrovimab and bamlanivimab, sotrovimab activity against the variants of concern was still maintained.

2.4.3. Pharmacokinetics

Two ELISA methods (reports 2020N456711 and 2021N466078) have been developed to measure serum levels of sotrovimab in monkey serum. One was qualified for use in a non-GLP PK study in

Cynomolgus monkeys, whereas the latter was validated for use in the 2 week repeat dose study in cynomolgus monkeys. Acceptable precision and accuracy were demonstrated.

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 is considered fit for purpose.

PK parameters were evaluated following a single administration of sotrovimab (5 mg/kg) IV in cynomolgus monkeys (2020N456684). Cmax following a single dose of 5 mg/kg sotrovimab in cynomolgus monkeys was 121 µg/mL. The estimated volume of distribution was 89.6 mL/kg, indicating limited distribution outside the vascular space, which is consistent with other IgGs. The mean CL of sotrovimab was 3.87 mL/day/kg. Sotrovimab had a long T1/2 of 17.7 days. The low CL and long T1/2 observed for sotrovimab is consistent with the addition of the half-life extending LS mutation [Ko, 2014]. No marked sex differences in PK parameters were observed. No ADA's were detected in this study.

Please refer to Toxicology section for the TK following the repeat-dose study in cynomolgus monkeys (2 administrations one week apart).

No standard studies of distribution were performed. Based on the PK iv study a volume of distribution of 89.6 ml/Kg was measured suggesting limited distribution beyond the blood compartment. The Applicant has suggested that the "LS" modification in the Fc domain of the antibody enhances its distribution to the respiratory mucosa. This theory was further substantiated, with the submission of a tissue biodistribution study (report 2021N472605). This study suggests 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.

No studies have been performed with respect to metabolism or excretion, which is in line with the relevant guideline (ICH S6 (R1)). As a monoclonal antibody sotrovimab will be eliminated via catabolic pathways. Similarly, as a monoclonal antibody directed against a foreign host protein the potential to affect CYP expression and activity is negligible and therefore the absence of studies on pharmacokinetic drug interactions is acceptable.

2.4.4. Toxicology

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

2.4.4.1. Single dose toxicity

No single-dose toxicity study was performed.

2.4.4.2. Repeat dose toxicity

One IV repeat dose toxicity study was performed, in cynomolgus monkeys, administered two doses at 0 (vehicle control), 50, 150 and 500 mg/kg/dose, 7 days apart (report 2021N468234). The study is claimed to comply with GLP, however, as discussed previously, not OECD/MAD GLP compliant. The reversibility, persistence, or delayed occurrence of any toxicities were evaluated following a 105-day

recovery period (approximately 5 half-lives). The main study dosing phase animals were necropsied on Day 15 and the recovery animals were necropsied on Day 120. The test item, sotrovimab, was well tolerated under the current study, at doses of up to 500 mg/kg (NOAEL). No test item related clinical signs were noted. Safety pharmacology endpoints were included, and no changes to CNS observations, ECG monitoring nor respiratory function was reported.

2.4.4.3. Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were performed. This is acceptable for an exogenous target and in line with ICH S6 (R1).

2.4.4.4. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies were not conducted with sotrovimab in line with ICH S6 (R1).

No sotrovimab-related toxicity was identified in male or female reproductive organs in young (adolescent) male or female monkeys in the repeat-dose toxicity study (all males were sexually mature except one high dose male was peripubertal).

2.4.4.5. Toxicokinetic data

In the repeat-dose toxicity study, systemic exposure increased dose-proportionally in males and females on Days 1 and 8 as the dosage increased from 50 to 500 mg/kg. No marked sex difference in systemic exposure and no marked drug accumulation was observed at any dose level.

With respect to exposure, one female in the control group (1504) showed measurable levels of sotrovimab, however, the observed values were just above the LLOQ (50 ng/mL) and significantly below the levels measured for animals in the treated groups. This finding was considered due to contamination with trace amounts of sotrovimab. As the levels were close to the LOD and no other control animals were positive, the finding is considered not to have any impact on the study outcome.

Dose proportional increases in Cmax and AUC was observed from Day 1 to Day 8 (dosing day 2), which is expected based on the long half-life of sotrovimab (approximately 17 days). Antidrug antibodies were observed in 12 of 144 animals, including a negative control animal. The following exposure ratios of sotrovimab in monkeys and humans were presented.

Table 1: exposure ratios of sotrovimab in monkeys and human

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).

A margin of exposure of 53-fold the clinical exposure levels (AUC) has been estimated at the NOAEL of 500 mg/kg.

2.4.4.6. Local Tolerance

Local tolerance endpoints were included in the repeat dose study in cynomolgus monkeys (report 2021N468234). In addition, an intramuscular local tolerance study was performed in Göttingen minipigs (report 2021N470452), as this route of administration is also being considered for clinical route of administration. In this study, the animals received an IM injection of 4 ml. In Diehl et al, 2001, good practice injection volume of 0.25 ml/kg (and maximum 0.5 ml/kg) is described. As the animals were all 12.5 kg (larger than the protocol description of 5 to 12 kg) at the start of the study, the good practice injection volume would be 3.125 ml/injection site, and maximum 6.25 ml/ injection site. Hence the volume administered is within the maximum recommended volume. No test article related local tolerance observations were noted in neither the cynomolgus monkeys nor minipig study.

2.4.4.7. Other toxicity studies

Immunogenicity

Anti-sotrovimab antibodies (ADA) were found in the NHP repeat-dose toxicity study (report 2021N468234), It is agreed that the nonclinical setting is not necessarily predictive of potential immunogenicity in the clinical setting. The absence of any specific immunotoxicity studies is accepted.

Tissue cross-reactivity

Tissue cross-reactivity studies were performed using a full panel of both human and cynomolgus tissues, including placenta, (2020N456662 and 2020N457086 respectively) to test for off-target tissue binding of sotrovimab. In both studies a biotinylated version of sotrovimab was utilised to investigate the potential off-target binding at concentrations of 1 and 5 µg/ml. No binding of sotrovimab against any of 37 normal human tissues or 37 normal cynomolgus monkey tissues was noted. The viability of the tissue sections was confirmed as the positive control staining with an anti-CD31 antibody generated signal in all tissue sections. Furthermore, a positive signal for sotrovimab was seen in CHO+SARS-CoV-2-Spike cells suggesting that the biotinylated sotrovimab was suitable for immunohistochemical (IHC) use.

In addition, the Retrogenix Cell Microarray technology platform was utilised to test for potential cross-reactivity of sotrovimab against 66 selected embryo-foetal secreted or plasma membrane proteins (2021N468478). These were selected on the basis of evidence of their preferential expression in embryo-foetal tissue and expressed in HEK293 cells where the ability of 2, 5 or 20 µg/mL of sotrovimab to interact with the expressed protein was investigated. No specific interactions were noted for any of the proteins tested.

No specific binding was observed in either of the studies, neither in cynomolgus monkey tissues nor in human tissues or foetal proteins expressed in HEK-293 cells.

2.4.5. 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 which are classified as proteins are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.4.6. Discussion on non-clinical aspects

Pharmacology

Overall, the PD data presented indicate that sotrovimab is a human IgG1κ SARS-CoV-2 neutralising mAb against the spike protein of SARS-CoV-2.

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. The clinical relevance of this finding is unclear to date.

The basis for the acclaimed activity against variants of concern is based mainly on using only the pseudotyped virus neutralisation system; however, additional data is available with live virus for the alpha, beta and gamma variants. The pseudotyped virus data largely agrees with the live virus data in that no discernible difference was measured for the beta and gamma variants and a slight decrease in activity was seen for the alfa variant (~3 fold for EC50 value). Based on preliminary in vivo data from hamsters the Applicant has suggested that activity of sotrovimab is maintained against the UK variant, however, the provided data are incomplete and further data are awaited for this study. The final study report 2021N475485 should be provided once available (REC).

The reported EC50 of sotrovimab against the omicron (B.1.1.529) pseudotype was 336.4 ng/mL (PC-7831-0146), representing a 2.7-fold reduction in neutralising activity, compared to the Wuhan spike pseudotype. Due to the radical nature of the changes in the omicron spike, it is supported that results from assays employing authentic omicron SARS-CoV-2 would be valuable (REC).

In general, the proof of concept in vivo studies are limited. In most of the studies the endpoints assessed were weight loss and viral load. One of the in vivo studies did report positive effects on lung pathology, and in the other two studies performed, histopathological examinations were not performed, but decreased lung weights in treated animals (0.5 mg/kg and above) were decreased, suggesting decreased lung inflammation. In all instances, the treatment with sotrovimab (or surrogate) has been performed prior to infection with SARS-CoV-2. The Applicant has suggested that the intra-peritoneal dosing of the antibody on Day -1 prior to infection is reflective of a treatment

paradigm based on Cmax levels not being achieved until 24-36 hours post-dosing. Whilst this may be the time frame for which Cmax is achieved, exposure potentially within the effective activity range will be seen prior to the subsequent infection in these studies. Therefore, the relevance of the in vivo studies to the clinical indication for the treatment of COVID-19 is somewhat limited. However, it is acknowledged that they do provide some proof of the potential activity of sotrovimab and ultimately the clinical data will be decisive in determining whether the product is efficacious or not.

Based on the totality of the data in vitro and in vivo data, it can be agreed that the risk of ADE appears low. There are no concerns identified in the safety pharmacology studies, which were performed as part of the repeat dose toxicity studies.

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

The toxicology package is in-line with the requirements of ICH S6 (R1) for a monoclonal antibody directed against a non-endogenous epitope. In the repeat dose study in NHP, the top dose of 500 mg/kg was deemed to be the NOAEL. A margin of exposure of 53-fold was calculated. This is to be updated once final PK data from the clinical setting has been generated. The repeat dose toxicity studies and the tissue cross-reactivity studies were performed in a non-MAD/OECD member country, there is no evidence that they were not performed in compliance with GLP regulations. Taking this into account as well as the relevant GLP inspections from an EU GLP monitoring authority it is proposed that no further inspections of the studies are required, and the studies can be considered supportive for the MAA.

No genotoxicity, carcinogenicity and DART studies have been conducted in line with ICH S6 guidance

2.4.7. Conclusion on the non-clinical aspects

Overall, the non-clinical development programme is limited though it is sufficient to support the marketing authorisation for sotrovimab.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

No routine GCP inspection was conducted for this application and no issues and/or concerns that would warrant the need for a GCP inspection were identified in the course of the assessment of the clinical data submitted in support of the application. This is in addition to the listing of any GCP inspections conducted, with the respective reports, the standard statement that the Applicant claimed GCP

compliance of all trials included in the application and the statement of compliance with Directive 2001/20/EC for trials conducted outside the EU.

- **Tabular overview of clinical studies**

VIR-7831-5001 (214367, also known as COMET-ICE) is the single pivotal study supporting this Marketing Authorisation Application (MAA). COMET-ICE is a randomised, double-blind, multi-centre, placebo-controlled trial of sotrovimab for the early treatment of COVID-19 in non-hospitalised participants. Below **Table *2*** shows in addition ongoing studies with sotrovimab for the treatment of COVID-19.

Table 2: Description of Clinical Efficacy and safety studies for treatment of COVID-19

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	Non-hospitalized adults with confirmed COVID-19	Hospitalized adults who have had COVID-19 symptoms less than or equal to 12 days,	Participants aged 12 years and older with mild/moderate COVID-19 at high risk	Non-hospitalized adults with mild-to-moderate COVID-19 and who had their

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)
	symptoms) at risk of disease progression	(mild/moderate, early disease with ≤7 days symptoms)	with or without end-stage organ failure or dysfunction	of disease progression	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	18 February 2021 (study ongoing)	16 December 2020 (01 March 2021 DSMB recommended recruitment in the sotrovimab sub-	10 June 2021 (Study ongoing)	The combination arms (bamlanivimab + sotrovimab arm) started on 25 January 2021, follow-up is ongoing

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)
	randomized participants will continue to be followed until their Week 24 visit [end of study] or early withdrawal)		protocol should cease, and follow-up of participants already randomized is ongoing)		

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Sotrovimab (VIR-7831, GSK4182136) is a human IgG1 kappa (IgG1κ) SARS-CoV-2 neutralising monoclonal antibody (mAb) with a LS modification to extend half-life.

The clinical pharmacology including immunogenicity of sotrovimab has been studied in the single pivotal COMET-ICE study as secondary objective.

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. Full data will be reported in the Week 24 analysis clinical study report (CSR). The Lead-in phase served as the first-in-human (FIH) assessment and included intense PK sampling in 10 sotrovimab treated subjects. Sparse sampling from 363 participants in the Expansion phase is available to date. Approximately 75% of ADA data (screening, confirmatory) through Day 29 are available along with available titers.

Pharmacokinetics data were analysed by non-compartmental analysis and a preliminary IV population PK model was developed to investigate the impact of covariates. Covariates investigated included demography (age, race, gender, ethnicity), country, morphology (body weight, height, BMI), disease (congestive heart failure group, chronic kidney disease group, diabetes group, renal impairment group), duration of symptoms, glomerular filtration rate, ADA at Day 29, hepatic markers (total bilirubin, ALT, AST, direct bilirubin, albumin), dexamethasone co-administration within 28 days and baseline viral load.

The single 500 mg IV dose is based on non-clinical data aimed to maintain serum levels highly above lung-tissue adjusted EC90 in the patients for 28 days.

Analytical methods

Concentrations of sotrovimab (VIR-7831, GSK4182136) in patient sera were quantitated by capture ELISA, using capture and detection antibodies which are specific for sotrovimab (electrochemiluminescence immunoassay performed at Syneos Health, San Francisco, CA; method TM.3184).

Anti-drug antibodies (ADA) against sotrovimab in patient sera were semi-quantitated using bridging ELISA (electrochemiluminescence bridging immunoassay performed at Syneos Health, Princeton, NJ; method TM.3002).

Viral loads in nasopharyngeal swabs were measured using quantitative RT-PCR developed and validated by Covance Central Laboratory services (assay uses primer pairs and probes based on the CDC's qualitative 2019-nCoV EUA Assay).

The antigenic type of SARS-CoV-2 causing disease in sotrovimab-treated patients as well as emergence of SARS-CoV-2 spike variants during sotrovimab treatment were monitored by sequencing

of the spike gene from SARS-CoV-2 RNA found in nasopharyngeal swabs (Illumina Mi-Seq platform, developed and verified at DDL Diagnostic Laboratory, Rijswijk, the Netherlands).

The analytical approaches employed in the PK assays above are well established and fit-for-purpose.

Generally, the validations of serological assays followed EMA guideline on validation of bioanalytical methods and immunogenicity assessment of monoclonal antibodies. As regards the sequencing method used to type SARS-CoV-2 in patients' samples, the technical characteristics documented in the DDL Diagnostics verification report are assessed as being scientifically well justified and adequate.

Pharmacokinetic data analysis

PK parameters for sotrovimab was calculated using standard non-compartmental methods and actual sampling times: 1, 2, 6, and 12 hr post infusion + Day 2, 5, 8, 15, 29, 43, 57, 85, 141 and 169) to characterize the PK after a single dose administration IV. Parameters included, but were not limited to Cmax, Clast, Tmax, Tlast, AUCinf, AUClast, %AUCexp, t1/2, λz, Vz, Vss, CL, and were listed and summarised using descriptive statistics. The PK data for the non-compartmental analysis consist of data from the COMET-ICE study with extensive PK sampling in nine subjects and sparse PK sampling from 363 subjects. PK sampling will continue until 6 months post-dose.

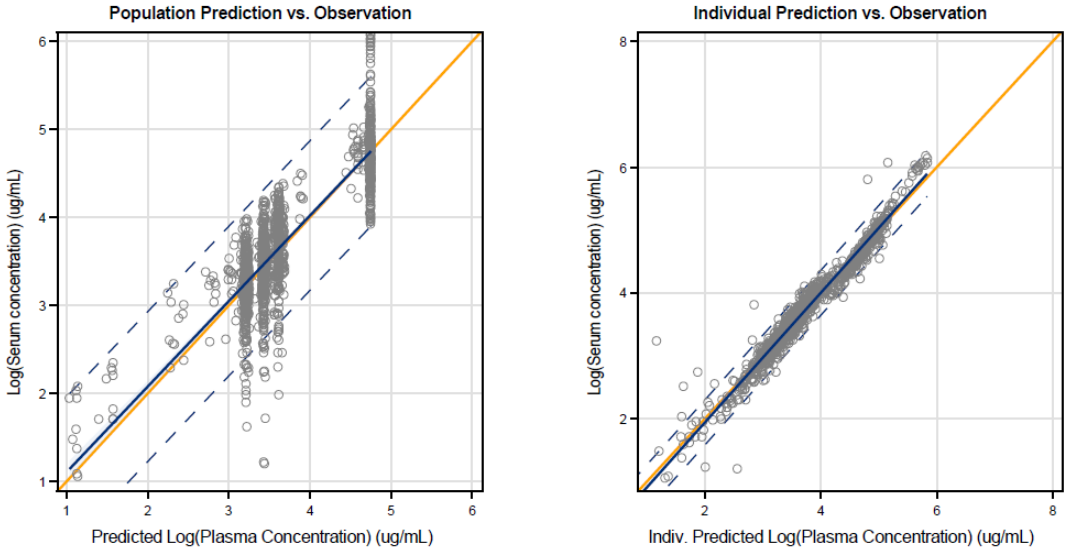
Population PK

A total of 1466 sotrovimab concentration values, obtained from 476 participants, were available to date and were analysed in the population PK analysis.

The pharmacokinetics of IV sotrovimab was well-described by a two-compartment model with first-order elimination parameterised in terms of both macro-constants and clearances and volumes.

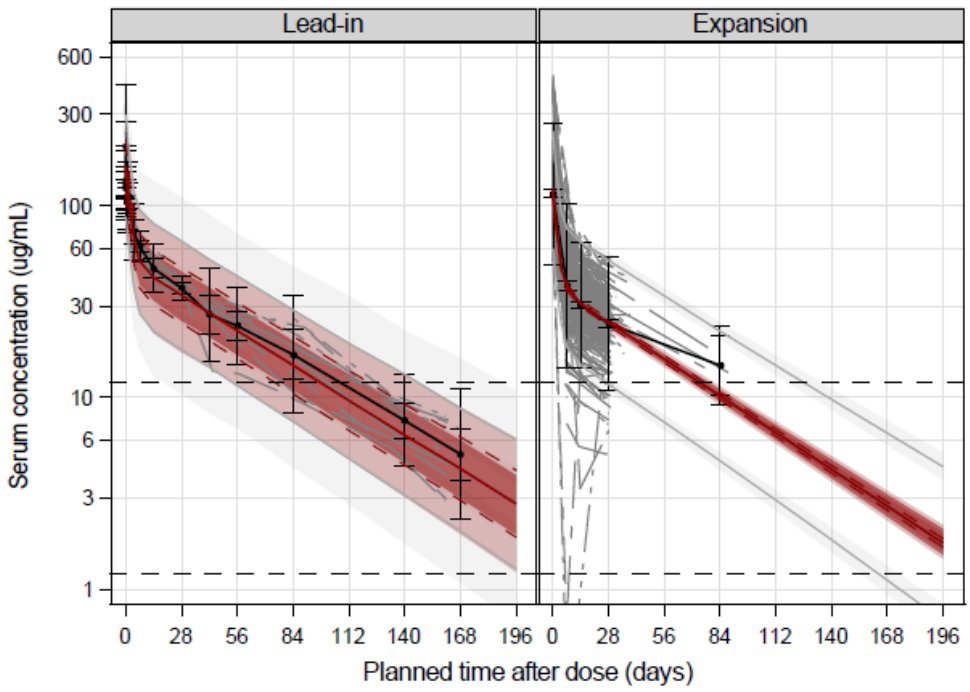
Model goodness of fit, as demonstrated by conventional plots and Normal Prediction Distribution Error (NPDE), are adequate and shown in ***Figure 3*** below.

Figure 3: Goodness of fit plots (regression)



Final PK model performance was also assessed using Visual Predictive Check (VPC) in Figure below. The model underpredicts in elimination phase but since treatment is a single dose this is not expected to have any clinical relevance.

Figure 4: Observed and predicted sotrovimab serum concentration-time profile (Geometric Mean (95% CI))



2-cmp IV bolus model with fixed allometry, 1000 simulations with propagation of parameter uncertainty
Median P5/P95 of geometric mean and 95% confidence limits indicated. Tissue-adjusted IC90 = 1.2ug/mL and 10xIC90 indicted

Body weight was incorporated into the model using physiological allometry with fixed allometric exponents of -1 (for A and B) and -0.25 (for Alpha and Beta). This translates to allometric exponents of 0.75 and unity for clearance and volumes, respectively. BMI was additionally incorporated in the model using a fixed power of 0.75 on all parameters (A, B, Alpha, and Beta) to further adjust for obesity and retain the typical scaling of clearance with body weight. Further adjustment to account for the two different populations (Lead-in vs. Expansion phase) was included as a fixed effect to describe the difference in demographics between populations. Between-participant variability was included for intercept PK parameters A and B as exponential random effects. An exponential residual error model was used to describe intra-individual variability.

Population PK parameter estimates in participants with COVID-19 are listed below.

Table 3: Population PK parameter estimates for sotrovimab IV population PK in participants with COVID-19

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

$A_i = (1+LNR[Lead\text{-}in])*TVA \exp(-LOG[BWT/87]+0.75*LOG[BMI/32] + b_1)$

$B_i = (1+LNR[Lead\text{-}in])*TVB \exp(-LOG[BWT/87]+0.75*LOG[BMI/32] + b_2)$

$ALPHi = ALPH*\exp(0.25*LOG(BWT/87)+0.75*LOG(BMI/32))$

$BETAi = BETA*\exp(0.25*LOG(BWT/87)+0.75*LOG(BMI/32))$

$CLi = ALPHi\ BETAi/(Ai\ BETAi + Bi\ ALPHAi)$

$Vdssi = (Ai\ BETAi^2+Bi\ ALPHi^2)/(Ai\ BETAi + Bi*ALPHi)^2$

$Thalf(ALPHi) = log(2)/ALPHi$ (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)

Source: m5.3.3.5 Population PK Report Table 2

For an 87 kg subject, sotrovimab has a systemic clearance of 0.192 L/day and distributes into a central volume of 4.28 L and a total volume of 11.5 L. The terminal-phase half-life of sotrovimab is 44.3 days.

A log-linear statistical model provided excellent agreement with both data and PK model, as shown in Figure 3. As per the population-PK model, only body weight and body mass index are significant determinants of exposure (**Table 3**).

Figure 5: Observed and predicted sotrovimab D29 Serum concentration boxplot (Mean, Median, IQR and 95% CI)

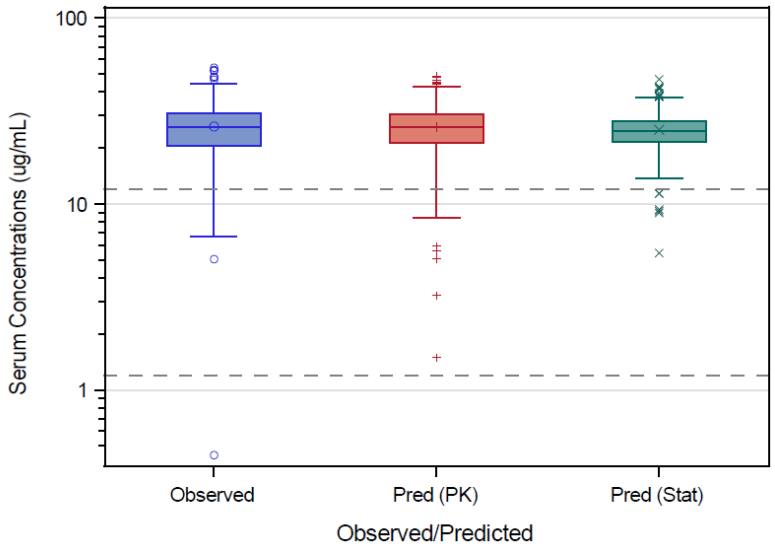


Table 4: Adjusted mean exposure ratios for bodyweight, age, renal and hepatic impairment

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

Absorption

Sotrovimab is administered by IV infusion and bioavailability is 100%.

The geometric mean Cmax following a 1 hour IV infusion was 117.6 µg/mL (N = 290, CV% 46.5), and the geometric mean Day 29 concentration was 24.5 µg/mL (N = 372, CV% 42.4).

Cmax after 500 mg single IV dose was observed at the end of the infusion with a mean value of 219 µg/mL in the Lead-in phase. The mean serum level on Day 29 was 37.2 µg/mL.

Distribution

Sotrovimab is expected to distribute as for endogenous IgG. 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).

Elimination

The degradation of sotrovimab is expected to be by non-specific proteolytic enzymes as well-known from other monoclonal IgG antibodies. Sotrovimab is not excreted renally.

Based on non-compartmental analysis of intensive PK data, the mean systemic clearance was 125 mL/day. Systemic clearance estimated in the Pop PK analysis was 0.192 L/day for a typical participant. The median terminal-phase elimination half-life was 48.8 days.

Dose proportionality and time dependencies

Only one dose, 500 mg IV, as a single dose has been investigated. It is therefore not known if the PK of sotrovimab is dose proportional. No multiple dose administration has been studied, so the potential for accumulation or time dependent PK is unknown.

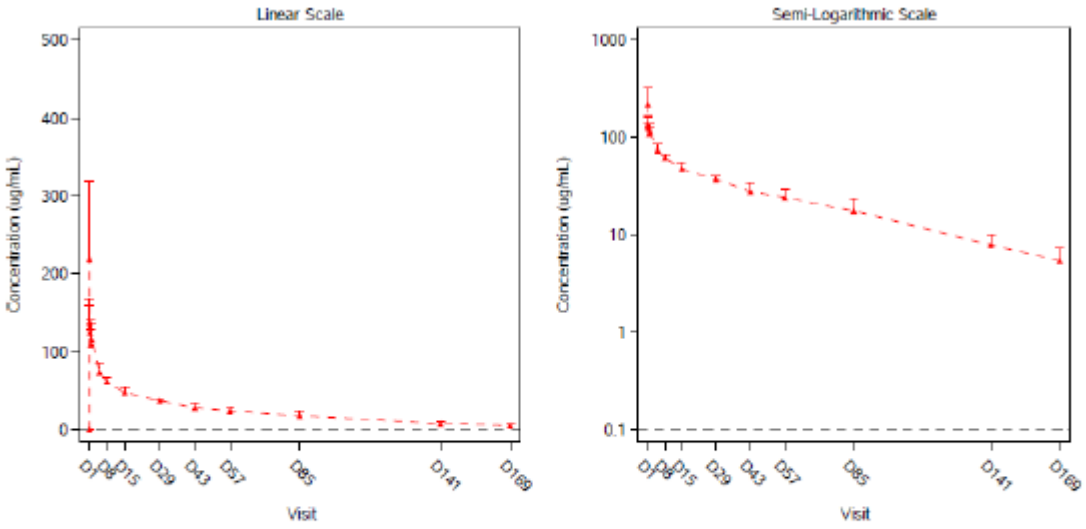
Variability

Estimates of within and between-subject variability were moderate, and 50% BSV on A and 38% BSV on B.

PK in target population

No studies have been conducted in healthy participants. All available human PK data are from the target population, i.e. non-hospitalised participants with mild/moderate COVID-19 and who were at risk for progression of disease treated with sotrovimab 500 mg infused over 60 minutes. PK parameters for sotrovimab are based on actual times and the mean PK profile are presented in **Figure 6** and **Table 5**, respectively.

Figure 6: Mean (+SD) sotrovimab serum concentration-time plots (linear and semi-log): Lead-in



Source: Figure 5.2,
Note: LLQ=0.1 µg/mL. Excludes anomalous concentrations identified as sampling errors by the clinical pharmacologist.
Data is based on 1-hour infusion time.

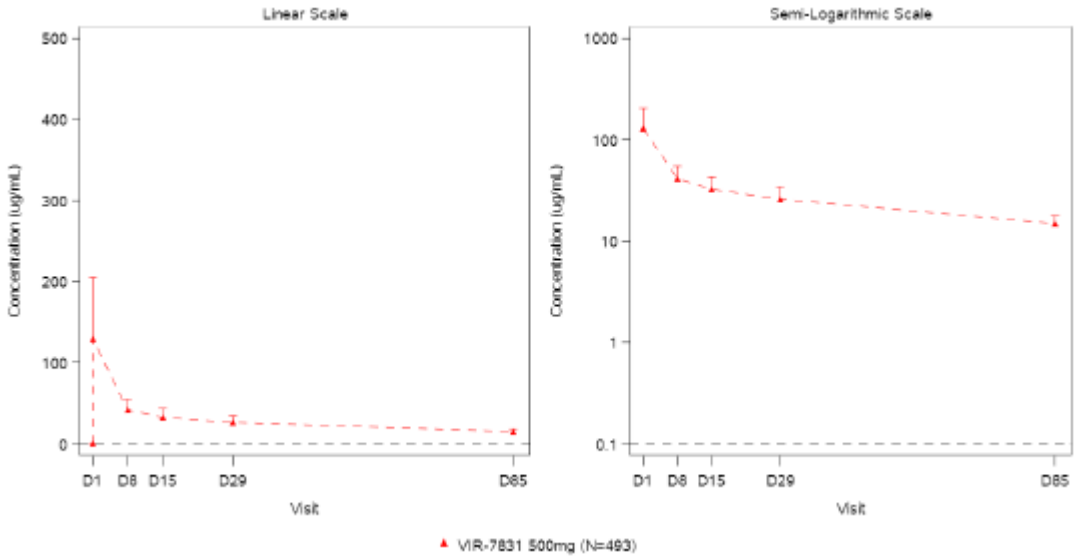
Table 5: Sotrovimab PK parameters following a 500mg IV dose

Parameter	Dose 500 mg (N = 9[a])
C_{max}, µg/mL	219 (45.5)
T_{max}, day	0.04 (0.04, 0.05)
C_{last}, µg/mL	5.41 (37.2)
T_{last}, day	161 (160, 167)
AUC_{D1-29}, day*µg/mL	1529 (9.6)
AUC_{last}, day*µg/mL	3714 (14.5)
AUC % Extrapolated	9.4 (37.9)
AUC_{inf}, day*µg/mL	4116 (16.9)
CL (mL/day)	125 (17.9)
V_z, L	8.76 (15.7)
V_{ss}, L	8.1 (11.1)
$t_{1/2}$, day	48.8 (37.8, 59.4)

Parameters are reported as mean (%CV) except for T_{max}, T_{last} and $t_{1/2}$, which are presented as median (min, max).
Data is based on 1-hour infusion time.
[a] N=8 for AUC_{D1-29} as participant 10016 was missing all PK samples prior to Study Day 5
Source: Table 5.4

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 8. The mean serum concentration of sotrovimab on study Day 29 is 25.8 µg/mL.

Figure 7: Mean (+SD) sotrovimab serum concentration-time plots (linear and semi-log): Expansion Phase



Special populations

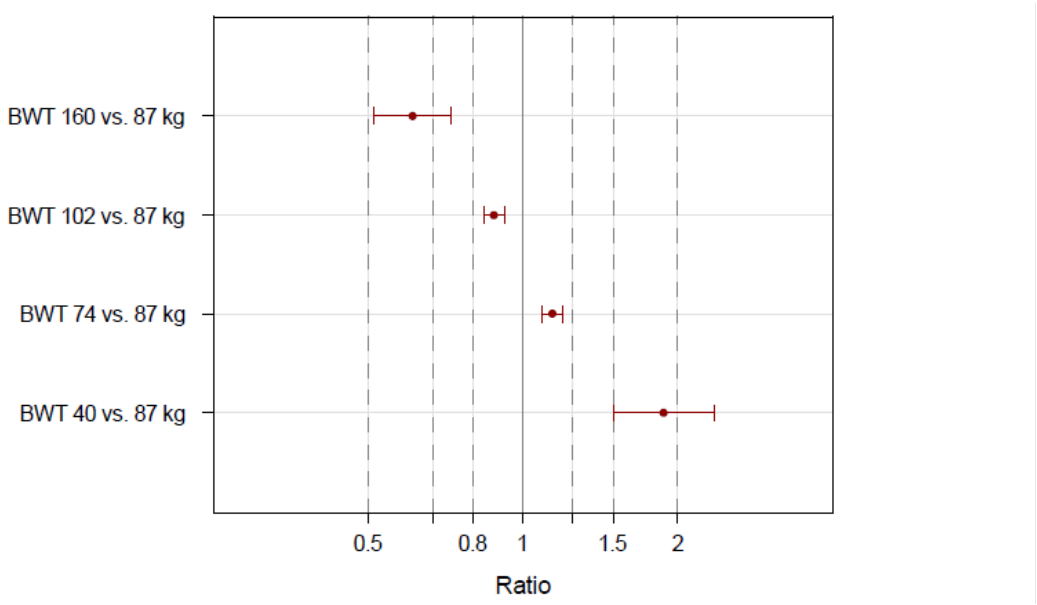
No dedicated studies were conducted to evaluate PK of sotrovimab in special populations. No intrinsic or extrinsic factors were found to have a clinically relevant effect on PK sotrovimab based on pop PK analysis.

There is no apparent effect of renal impairment on sotrovimab clearance. The majority of subjects (95 %) in COMET-ICE had normal renal function or mild renal impairment and only two subjects with severe renal impairment were included. However, for single dose administration of a monoclonal antibody it is agreed that data are adequate to recommend that no dose adjustment is required in patients with renal impairment.

The impact of markers of liver inflammation such as bilirubin and aspartate aminotransferase (AST) as well as mild to moderate elevations in alanine aminotransferase on the PK of sotrovimab were evaluated in the population PK analysis. Hepatic markers were not significant covariates of sotrovimab exposure. There is no apparent effect of mild or moderate hepatic impairment on sotrovimab clearance. The majority of subjects (98 %) in COMET-ICE had normal hepatic function or mild hepatic impairment and only one subject with severe hepatic impairment were included.

Body weight is a significant determinant of sotrovimab exposure. Over a body weight range of 40 – 160 kg the magnitude of effect of body weight on sotrovimab exposure (serum concentration) is 1.88 - 0.61 (for fixed allometric power of 0.75) times the reference exposure for 87 kg. Additional ratios for IQR are provided in **Figure 8**.

Figure 8: adjusted mean exposure ratio by bodyweight (Geometric Mean (95% CI))



Body mass index (BMI) was also included as determinant of sotrovimab exposure on physiological grounds. Over a BMI range of 25– 40, the magnitude of effect of BMI on sotrovimab exposure is 0.90 - 1.10 (for fixed allometric power of 0.75) times the reference exposure for 32 kg/m^2 BMI.

Of the 503 subjects in the Pop PK analyses, 99 were > 64 years of age and 5 > 84 years of age. Age did not have an impact on clearance, however few of the very elderly were included.

Sotrovimab IV pharmacokinetics has not been evaluated in paediatric participants (less than 18 years). The dosing in adolescents is proposed based on conventional, long-established, allometric assumptions, with scaling powers for volume and clearance of 1.0 and 0.75, respectively.

Ten subjects out of 503 were ADA positive on day 29. Anti-sotrovimab antibodies on day 29 does not appear to have an impact on clearance. However, this is based on the limited number of subjects with ADA at day 29. With a single dose administration presence of ADAs is not a concern.

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.

2.5.2.2. Pharmacodynamics

Mechanism of action

Sotrovimab (VIR-7831, GSK4182136) is a human IgG1 kappa (IgG1κ) SARS-CoV-2 neutralising monoclonal antibody (mAb) derived from the parental human mAb S309, which was selected from memory B cells of an individual who survived SARS-CoV-1 infection in 2003 based on the mAb's ability to cross-neutralise SARS-CoV-2. Sotrovimab binds to a highly conserved spike protein epitope which is present in SARS-CoV-1 as well as SARS-CoV-2.

The epitope comprises approx. 23 non-contiguous amino acids in the receptor-binding part of the spike protein; it is distinct from epitopes targeted by other anti-SARS-CoV-2 mAbs in clinical use such as bamlanivimab (LY-CoV555) and casirivimab (REGN10933).

The epitope has minimal overlap with the binding site of the ACE2 receptor on the receptor-binding part of the spike protein (RBD), and the mAb does not compete with ACE2 for RBD binding (assayed on immobilized ACE2 by biolayer inferometry, using full-length and Fab formats).

Nevertheless, sotrovimab neutralizes SARS-CoV-2 in vitro with a potency commensurate with clinical use (EC50 values of 58.1 - 100.1 ng/mL and 24.06 - 104.46 ng/mL using authentic SARS-CoV-2 and pseudotyped vesicular stomatitis virus particles, respectively).

The Applicant proposed that cross-linking of spike trimers on virions and aggregation of virions might contribute to neutralization. Also, the N343 glycan contained in the sotrovimab epitope has been suggested to be involved in maintaining the spike protein in the up conformation which is required for binding to the ACE2 receptor, i.e., in native virions, mAb binding to the epitope site might theoretically cause allosteric changes in the spike protein which interfere with binding to the receptor.

The mAb is expected to exhibit essentially the normal, full range of Fc-mediated effector functions, which is supported by preclinical data.

In the hamster model of SARS-CoV-2 infection, antibody-dependent enhancement of infection was not seen at any dose evaluated, including subneutralizing doses.

Preclinical toxicology supports that despite the conserved nature of the epitope, the mAb is not polyreactive (clean results from tissue cross-reactivity studies using normal monkey and human tissues including placenta, and protein binding assay using a protein array enriched for human embryofetal proteins).

Assessment of barrier against development of monoclonal antibody resistance mutations (MARMs) in preclinical studies:

Analysis of all spike sequences available in the GISAID database was confirmed that the approx. 23 amino acids making up the sotrovimab epitope are > 99.98% conserved.

Currently circulating SARS-CoV-2 variants of concern do not carry mutations in the sotrovimab epitope, and accordingly, neutralizing activity is essentially retained against currently circulating variants of concern and variants of interest (alpha, alpha+E484K, beta, delta, gamma, epsilon, iota, eta and others; at most approx. 4 to 5-fold reductions in neutralization potency using authentic SARS-CoV-2 as well as pseudotyped virus particles).

The slight reduction in neutralization potency against variants of concern was taken into account when selecting the clinical dose of 500 mg.

Using two orthogonal approaches (targeted mutation of sotrovimab epitope site and selection of escape mutants by serial passage in presence of mAb in vitro), it was found that mutations at sotrovimab spike epitope positions P337 and E340 have very strong negative impact on the in vitro neutralizing potency of sotrovimab in vitro (essentially loss of neutralization, depending on the biochemical nature of mutations).

The effect of the P337 and E340 MARMs on Fc-mediated effects has not been investigated. The P337L spike mutation has been detected in one participant in the sotrovimab arm of the COMET-ICE trial. The P337L spike mutation is known to confer resistance to sotrovimab based on the preclinical data.

Cross-neutralization and interference with other anti-SARS-CoV-2 mAbs in clinical use (preclinical in vitro data,* reports *2021N466446 and 2021N470273):

Sotrovimab used on its own effectively neutralized pseudotyped viruses expressing spike monoclonal antibody resistance mutation MARMs that confer reduced susceptibility to as bamlanivimab (LY-CoV555), casirivimab (REGN10933) and imdevimab (REGN10987).

Specifically, sotrovimab neutralization potency was minimally reduced for 18 of the 19 MARMs tested (reductions in EC50 values < 3-fold).

Reciprocally, the E340A and E340K mutations identified as conferring resistance to sotrovimab neutralization were fully susceptible to bamlanivimab.

Finally, a combination of sotrovimab and bamlanivimab (LY-CoV555) combination was then assessed on a panel of the most concerning antigenic variants of SARS-CoV-2 currently circulating (mixed at a ratio of 1 ug sotrovimab: 1.4 ug bamlanivimab).

As expected, based on the preclinical results outlined above, when used alone, sotrovimab maintained activity against all antigenic variants.

In contrast, several antigenic variants were resistant against bamlanivimab neutralization, in agreement with the known reactivity profile of the antibody.

The combination of sotrovimab + bamlanivimab neutralized all variants similarly to sotrovimab alone; i.e., no interference was observed between sotrovimab and bamlanivimab (LY-CoV555) in vitro.

Changes in nasopharyngeal virus loads over time after sotrovimab or placebo treatment (pivotal COMET-ICE trial):

Based on the available data, distribution of baseline viral load was similar across treatment arms for all baseline viral load cut-off groups. While interpretation is limited due to the low number of participants across categories, the data generally show that the majority of participants had a baseline viral load of >1E6 copies/mL and the mean change from baseline decline was greater in participants with the higher baseline viral load cut-offs (see table below, panel B).

Change from baseline in viral load in nasal secretions by qRT-PCR at day 8 was a secondary efficacy endpoint in the trial.

The mean decline from baseline in viral load at day 8 was statistically significantly greater in sotrovimab-treated participants compared to that in placebo-treated participants (p=0.003; see table below, panel A).

The difference in viral load for sotrovimab compared with placebo was -0.474, -0.251, and -0.121 log 10 copies/mL at day 5, day 8, and day 11, respectively (see table below, panel A).

These greater declines in viral loads in sotrovimab-treated patients were statistically significant at day 5 (p<0.001) and day 8 (p=0.003).

Table 6: (A) Summary of viral load changes from baseline to day 8 in placebo and sotrovimab treatment arms (secondary efficacy endpoint from COMET-ICE); (B) The data from panel A stratified by baseline viral load (determined by quantitative RT-PCR on nasopharyngeal swabs).

A

	Placebo (N=385)	Sotrovimab (500 mg IV) (N=369)
Baseline (log 10 copies/mL)		
n	385	369
Mean (standard deviation)	6.645 (1.6632)	6.535 (1.6331)
Day 8 viral load (log 10 copies/mL)		
n	323	316
Mean (standard deviation)	4.276 (1.3646)	3.989 (1.1913)
Day 8 change from baseline (log 10 copies/mL) [a]		
LS Mean Change from Baseline (SE)	-2.358 (0.0589)	-2.610 (0.0593)
95% CI	(-2.474, -2.243)	(-2.726, -2.493)
Difference (SE)	-0.251 (0.0835)	
95% CI	(-0.415, -0.087)	
p-value	0.003	

B

SARS-CoV-2 Viral Load (log 10 copies/mL)	Placebo (N=385)	Sotrovimab (500 mg IV) (N=369)
Baseline SARS-CoV-2 Viral Load (copies/mL): ≤log10^5 copies/mL		
n[a]	**66**	**55**
LS Mean (SE)	3.370 (0.1319)	3.194 (0.1436)
LS Mean Change from Baseline (SE)	-0.934 (0.1302)	-0.940 (0.1417)
95% CI	(-1.190, -0.679)	(-1.218, -0.662)
Difference (SE)	-0.006 (0.1922)	
95% CI	(-0.383, 0.372)	
Baseline SARS-CoV-2 Viral Load (copies/mL): >log10^5 copies/mL- ≤log 10^6		
n[a]	**50**	**59**
LS Mean (SE)	3.755 (0.1550)	3.748 (0.1449)
LS Mean Change from Baseline (SE)	-1.786 (0.1529)	-1.745 (0.1429)
95% CI	(-2.086, -1.485)	(-2.026, -1.465)
Difference (SE)	0.040 (0.2093)	
95% CI	(-0.371, 0.451)	
Baseline SARS-CoV-2 Viral Load (copies/mL): >log10^6 copies/mL- log 10^7		
n[a]	**47**	**60**
LS Mean (SE)	4.211 (0.1583)	3.799 (0.1389)
LS Mean Change from Baseline (SE)	-2.325 (0.1562)	-2.689 (0.1371)
95% CI	(-2.632, -2.019)	(-2.958, -2.420)
Difference (SE)	-0.364 (0.2078)	
95% CI	(-0.772, 0.044)	
Baseline SARS-CoV-2 Viral Load (copies/mL): >log10^7 copies/mL		
n[a]	**160**	**142**
LS Mean (SE)	4.816 (0.0874)	4.454 (0.0925)
LS Mean Change from Baseline (SE)	-3.298 (0.0862)	-3.612 (0.0913)
95% CI	(-3.467, -3.129)	(-3.791, -3.433)
Difference (SE)	-0.314 (0.1254)	
95% CI	(-0.560, -0.068)	

Viral resistance analysis in pivotal COMET-ICE phase II/III trial:

The resistance analysis in the report is based on ~90% of viral load data from the study population available in the day 29 analysis data cut-off (27 April 2021), corresponding to ~38% of total participants who qualify for sequence analysis (273 of 711 participants).

Specifically, at the time of this initial virology analysis, results from 259 participants at baseline were available (sotrovimab 127; placebo 132) and results from 80 participants' post-baseline samples were available (sotrovimab 45; placebo 35) and included in the report.

Resistance analysis is currently limited by the availability of viral load data due to analysis delays at the central laboratory.

The main findings were:

- Of the approx. 5-10 SARS-CoV-2 variants of concern currently known to circulate in humans, only two occurred in the trial (alpha and epsilon variants). Eleven participants carried the alpha SARS-CoV-2 variant of concern (5 sotrovimab; 6 placebo; B.1.1.7, first detected in the UK), and 12 participants carried the epsilon SARS-CoV-2 variant of concern (5 sotrovimab; 7 placebo; B.1.427, first detected in California).
- With the exception of the 2 participants who met the primary clinical outcome for progression (sotrovimab arm, epsilon variant; placebo arm, alpha variant), all participants with variants of concern experienced declines in SARS-CoV-2 viral load through day 29.
- Formal analysis of treatment-emergent epitope variants (defined as variants detected in post-baseline samples but not detected in corresponding baseline samples), identified treatment-emergent epitope variants in seven patients in the sotrovimab arm (E340K in two patients, S359G in two patients, A344V in one patient, C361T in one patient, and K356R in one patient); none treatment-emergent epitope variants were detected in the placebo arm.
- Phenotypic analysis of the abovementioned treatment-emergent epitope variants confirmed that only E340K is associated with loss of sotrovimab neutralization (as expected based in the preclinical data, see section above). In agreement with this, while E340K epitope variants were dominant in sequences obtained from individual nasopharyngeal swabs, S359G, A344V, C361T and K356R epitope variants comprised the minority of sequences obtained from individual swabs from individual patients (<15%), indicating these variants were not significantly enriched in the SARS-CoV-2 quasispecies populations present in patients' nasopharynges).
- Thus, development of sotrovimab resistance mutants (MARMs, specifically E340K) was detected in 2 of 35 participants in the sotrovimab arm, and none in the placebo arm.
- With the exception of 1 participant in the sotrovimab arm who met the criteria for clinical progression (E340K variant), all participants with variants in the sotrovimab epitope, regardless of whether variants were detected before or after baseline, experienced declines in SARS-CoV-2 viral load through day 29.
- One participant did not have viral load samples available past day 15.

Exposure-response relationship

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

During clinical development, immunogenicity was assessed using a risk-based bioanalytical strategy.

A multi-tier approach was used to analyse the samples for ADA. Samples were first analysed in a screening assay to detect the presence of antibodies directly binding to sotrovimab. Samples that were determined to be positive in the screening assay were then tested in the confirmatory assay with an excess of 10 ug/mL of sotrovimab to confirm specificity to the drug. All confirmed positive samples were analysed in a titration assay and reported as positive. The titration assay provides a quasi-quantitative assessment of relative ADA response.

The incidence of post-treatment anti-sotrovimab antibodies has been low, with all titres near the sensitivity limit of the assay (≤160). To date, immunogenicity data are available for 75 % of participants. Seventeen participants were ADA positive at baseline and ten participants at day 29.

Of the ten patients ADA positive at Day 29, of which 4 were positive for ADA at baseline and showed no increase post-baseline. Thus, 6/10 were considered to have treatment-induced ADA. Two of the 6 were negative for ADA at baseline and 4 have not yet had a baseline sample analysed.

Table 7: Number of confirmed positive immunogenicity results for sotrovimab through Day 29 in COMET-ICE

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

Note: Summary presents the number of confirmed positive results out of the total number of screening results

Sotrovimab is administered as a single dose and the risk of clinical relevance of ADAs considered limited. In the Pop PK analysis, there was no indications of impact of ADAs on exposure. The detection of ADAs at baseline is at present not a clinical concern. There is no information regarding neutralizing ADAs (nABs).

Dose justification

No dose response study has been conducted. Only one dose of 500 mg has been investigated.

Sotrovimab neutralized SARS-CoV-2 live virus with an average 90% effective concentration (EC90) value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL)

A 500 mg IV dose has been selected since it is expected to ensure that sotrovimab concentrations in lung are maintained well above levels anticipated to be neutralising for the first 28 days after administration.

Based on the available PK, a 500 mg IV dose of sotrovimab is expected to maintain serum levels at or above 25x lung-tissue adjusted EC90 for 28 days in 50% of participants and at or above 15x lung-tissue adjusted EC90 for 28 days in 95% of participants; this is based on the EC90 (0.33 µg/mL) from the highest end of the EC90 range, and accounting for the lung: serum ratio for IgG. Human exposure following a 500 mg single IV dose is considerably lower than the NOAEL.

2.5.3. Discussion on clinical pharmacology

Sotrovimab is an Fc-engineered IgG1 monoclonal antibody with the addition of a LS modification. Treatment is a single 500 mg IV dose by infusion. The proposed indication is for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

The pharmacokinetics of sotrovimab has been studies in the single pivotal study, COMET-ICE, as secondary objective. PK data include extensive PK sampling in the lead in phase from nine subjects and sparse PK sampling from 363 subjects in the expansion phase. PK data up to day 29 are available to date, but PK sampling will continue up to day 169. Final PK results should be provided (REC).

PK has been investigated in the target population, i.e. non-hospitalised participants with mild/moderate COVID-19 and who were at risk for progression of disease.

Concentrations of sotrovimab in patient sera were quantitated by capture ELISA and Anti-drug antibodies (ADA) against sotrovimab in patient sera were semi-quantitated using bridging ELISA. Overall, the analytical methods are acceptable, have been adequately validated in line with regulatory guidance and are fit for purpose.

PK sampling per subjects was is deemed sufficient (1, 2, 6, and 12 hr post infusion + Day 2, 5, 8, 15, 29, 43, 57, 85, 141 and 169) to characterize the PK after a single dose administration IV.

Pharmacokinetics data were analysed by non-compartmental analysis and population PK analysis.

Sotrovimab is degraded by proteolytic enzymes, which are widely distributed in the body and not restricted to hepatic tissue. Sotrovimab, like other immunoglobulins, is not excreted renally.

Mean Cmax was 219 µg/mL following a 1-hr IV infusion and mean serum level on Day 29 is 37.2 µg/mL. The estimated steady-state volume of distribution was 8.1 L. Sotrovimab had a mean clearance of 125 mL/day and a median half-life of 48.8 days.

A preliminary IV population PK model was developed to evaluate sotrovimab PK with data from COMET-ICE and investigate the impact of covariates. Concentration values, obtained from 476 participants, were available to date and were analysed in the population PK analysis.

PK of sotrovimab appear adequately described by a two-compartment model with first order elimination. In the Pop PK report it is stated that a total of 503 participants (10 included in the Lead-in phase and 493 included in the Expansion phase) were planned to receive the drug, altogether 476 provided PK samples for analysis and were included in the sotrovimab population PK analysis data set.

Altogether, 57 samples with non-physiological results were excluded the VPCs show that the model underpredicts in elimination phase but since treatment is a single dose this is not expected to have any clinical relevance.

No dedicated studies were conducted to evaluate PK of sotrovimab in special populations, which is acceptable and has been adequately justified. The population PK model has been used to explore the impact of covariates and to inform on dosing recommendations in special populations. Covariates investigated included demography (age, race, gender, ethnicity), country, morphology (body weight, height, BMI), disease (congestive heart failure group, chronic kidney disease group, diabetes group, renal impairment group), duration of symptoms, glomerular filtration rate, ADA at Day 29, hepatic markers (total bilirubin, ALT, AST, direct bilirubin, albumin), dexamethasone co-administration within 28 days and baseline viral load.

Body weight was identified as a significant covariate as expected for a monoclonal antibody and had a factor 2 impact on exposure in both directions. The clinical impact is expected to be minor considering also the single dose treatment.

The dose-response relationship is unknown, since all subjects in the PK analysis have received the same dose. However, the magnitude of effect of body weight on sotrovimab exposure is not expected to be clinically relevant. The lower weight limit of 40 kg is consistent with other mAbs for the treatment of COVID-19.

Age, gender, race/ethnicity, the presence of anti-sotrovimab antibodies on day 29 and all other covariates included in the Pop PK analysis did not have an impact on sotrovimab clearance. Few very elderly were included.

Renal or hepatic impairment do not have an impact on sotrovimab PK and no dose adjustment is warranted.

Sotrovimab IV pharmacokinetics has not been evaluated in paediatric participants (less than 18 years). The proposed extrapolation to adolescents from 12 years of age weighing at least 40 kg is in line with comparable products.

Sotrovimab is not renally excreted or metabolised by CYP enzymes. Interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely. Drug-drug interactions are adequately reflected in the SmPC.

PK data are available form a single pivotal study with administration of sotrovimab as 500 mg IV single dose The PK of sotrovimab has overall been adequately described.

Assessment of barrier against development of monoclonal antibody resistance mutations (MARMs) in preclinical studies

Analysis of all spike sequences available in the GISAID database confirmed that the approx. 23 amino acids making up the sotrovimab epitope are > 99.98% conserved, as expected. In agreement with this, the neutralizing potency of sotrovimab was essentially maintained against a comprehensive panel of currently circulating SARS-CoV-2 variants of concern and variants of interest.

Using two orthogonal approaches (targeted mutation of sotrovimab epitope site and selection of escape mutants by serial passage in presence of mAb in vitro), sotrovimab spike epitope positions P337 and E340 were identified as key residues for development of MARMs (see under COMET-ICE viral resistance data below).

Cross-neutralization and interference with other anti-SARS-CoV-2 mAbs in clinical use (preclinical in vitro data)

MARMs (monoclonal antibody resistance mutants) that confer reduced susceptibility to bamlanivimab (LY-CoV555), casirivimab (REGN10933) and imdevimab (REGN10987) were sensitive to sotrovimab, and reciprocally, MARMs conferring reduced susceptibility to sotrovimab (E340A and E340K) remained sensitive to bamlanivimab. Also, when used in combination, sotrovimab and bamlanivimab (LY-CoV555) did not exhibit interference in in vitro neutralization assays.

These findings are expected based on the known epitope-specificity of the mAbs and are seen as positive as regards clinical use of sotrovimab.

Changes in nasopharyngeal virus loads over time after sotrovimab or placebo treatment (pivotal COMET-ICE trial)

The mean decline from baseline in viral load was consistently larger in the sotrovimab group, compared to placebo with greater declines in sotrovimab group at days 5, 8 and 11.

SARS-CoV-2 loads in upper airways are considered relevant for disease severity and progression, and this endpoint has been used in clinical studies for other anti-SARS-CoV-2 mAbs.

The results are in agreement with the mode-of-action of the mAb (quenching of viral replication by neutralization and/or clearance of virus by Fc-mediated effects) and considered to comprise a relevant secondary efficacy endpoint.

Viral resistance analysis in pivotal COMET-ICE phase II/III study

Due to the small size of the dataset, formal efficacy of sotrovimab against the alpha and epsilon variants cannot be assessed. Nevertheless, it is encouraging the exception of the 2 participants who met the primary clinical outcome for progression (sotrovimab arm, epsilon variant; placebo arm, alpha variant), all participants with variants of concern experienced declines in SARS-CoV-2 viral load through day 29. While sotrovimab exhibited a 4.1-fold reduction in neutralizing potency against the alpha variant in vitro, this was taken into consideration in setting the clinical dose of 500 mg, and lack of efficacy against alpha is not expected.

Development of sotrovimab resistance mutants (MARMs, specifically E340K, in agreement with preclinical studies mapping MARMs) was detected in 2 of 35 participants in the sotrovimab arm, and none in the placebo arm.

On one hand, MARMs can cause loss of efficacy because virus is no longer neutralized. On the other hand, MARMs may potentially negatively impact viral fitness. Also, sotrovimab exerts Fc-mediated effector functions, and the impact of E340 MARMs on the Fc-mediated functions of the mAb is unknown. Finally, the kinetics of MARM emergence is of relevance (slow emergence of MARMs may allow some natural protective immunity to be established, of course only in immuno-competent patients). Until more is known about the contribution of Fc-mediated effector functions to protective effects (no data is available on this), and until more experience is established with sotrovimab use in different patient populations, the clinical significance of the observed sotrovimab MARMs on disease outcomes cannot be predicted (may be negative or neutral, depending on clinical context and individual characteristics of patients).

Pending more/later data from COMET-ICE, it is encouraging that all participants with variants in the sotrovimab epitope, regardless of whether variants were detected before or after baseline, experienced declines in SARS-CoV-2 viral load through day 29 (determined by quantitative RT-PCR on nasopharyngeal swab material), and the occurrence of MARMs was relatively low (MARMs developed in 5.7% of treated patients by the formal analysis). Also, it is positive that in vitro neutralization data supports that sotrovimab MARMs remain sensitive to other mAbs in clinical use. Nevertheless, the issue of viral resistance is not resolved, and viral resistance and planned biomarker analyses should be completed for the material sampled in the COMET-ICE trial. It is understood from the preliminary COMET-ICE reports that this is realized by the Applicant, and the methods employed by the Applicant to monitor viral resistance are supported. Surveillance of viral resistance is expected to be part of routine pharmacovigilance activities. However, the delta variant currently predominates in the EU, and there are no clinical efficacy data for sotrovimab against delta due to the timing of the clinical study COMET-ICE. The pseudotyped VLP data do give good support to lack of any effect of the delta variant (and its subvariants) on the activity of sotrovimab. The neutralization data for authentic viruses support a conclusion that the antiviral activity of sotrovimab is maintained against the kappa and delta variants.

Exposure-response

COMET-ICE evaluated a single 500 mg IV dose of sotrovimab; therefore, no dose-effect relationship has been evaluated.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to sotrovimab following treatment. During clinical development, immunogenicity was assessed using a risk-based bioanalytical strategy. To date, immunogenicity data are available for 75 % of participants. Seventeen participants were ADA positive at baseline and ten participants at day 29.

Sotrovimab is administered as a single dose and the risk of clinical relevance of ADAs considered limited. In the Pop PK analysis, there was no indications of impact of ADAs on exposure, however, data are limited. The detection of ADAs at baseline is not a clinical concern.

There is no information regarding neutralizing ADAs (nABs). This is acceptable.

Immunogenicity has for now only been preliminary addressed. Immunogenicity assessment will continue in COMET-ICE.

At this time, since ADA will not be measured in routine use, there does not seem to be any point in mentioning development of ADA in the SmPC.

Dose rationale

The proposed 500 mg IV dose is based on preclinical data aimed to maintain serum levels highly above lung-tissue adjusted EC90 in the patients for 28 days. The dose rational and choice of dose for the clinical study is followed but since only one dose has been investigated, it remains an open question if this dose is optimal, both in terms of efficacy and safety. This is an obvious weakness of the clinical development program. It is acknowledged that human exposure following a 500 mg single IV dose is considerably lower than the NOAEL.

2.5.4. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of sotrovimab up to day 29 has been adequately described in the target population. The planned 24-weeks follow-up has not been completed yet and the following should be provided once available: final PK data, updated results on the analysis on variants.

2.5.5. Clinical efficacy

The efficacy programme comprises one pivotal trial, the COMET-ICE study. The dose finding study is based on preclinical data. Currently, two phase 2 trials and two phase 3 trials are ongoing, however efficacy data from those trials are not available yet. The trials are examining other drug substances, other administrations, other populations or combination treatment, hence the data from those studies is not considered relevant for efficacy. The studies are briefly described in the safety section.

Table 8: Summary table of COMET-ICE study methods

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(S)
VIR-7831-5001 (214367), (also known as COMET-ICE)	57 centers: Brazil: 6 Canada: 2 Spain: 3 Peru: 1 US: 45	First participant enrolled=27 August 2020, Last participant enrolled **11 March 2021** Screened: 1355 Randomized: 1057	Primary Objective: Evaluate the efficacy of sotrovimab in preventing progression of mild/moderate COVID-19	R, DB,PC	Adults with early mild/moderate COVID-19 at high risk of progression of disease based on presence of one or more risk factors	Randomised 1:1 to receive a single, IV dose of sotrovimab 500 mg or placebo, administered over 60 minutes	Total: 1057 placebo=529 sotrovimab=528	485M, 572F; 53 (17-96)	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

AC = Active control
BID = Twice daily
CPSR = Clinical Pharmacology Study Report
CSR = Clinical Study Report
DB = Double-blind
P = Placebo
PC = Placebo-controlled
PD = Pharmacodynamics
PG = Parallel Group
PK = Pharmacokinetics
R = Randomized
RD = Rising Dose
SB = Single-blind

2.5.5.1. Dose-response studies

No dose response study was conducted. The dose rationale is discussed in the Clinical Pharmacology section.

2.5.5.2. Main study

A single pivotal trial (COMET-ICE) provides data for the evaluation of efficacy. This study is a phase II/III, randomised, multi-centre, double-blind, placebo-controlled trial.

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, the trial was stopped due to efficacy and so 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.

The planned 24-weeks follow-up has not been completed yet. Those data will be provided in an amendment when the 24-weeks follow-up has been completed.

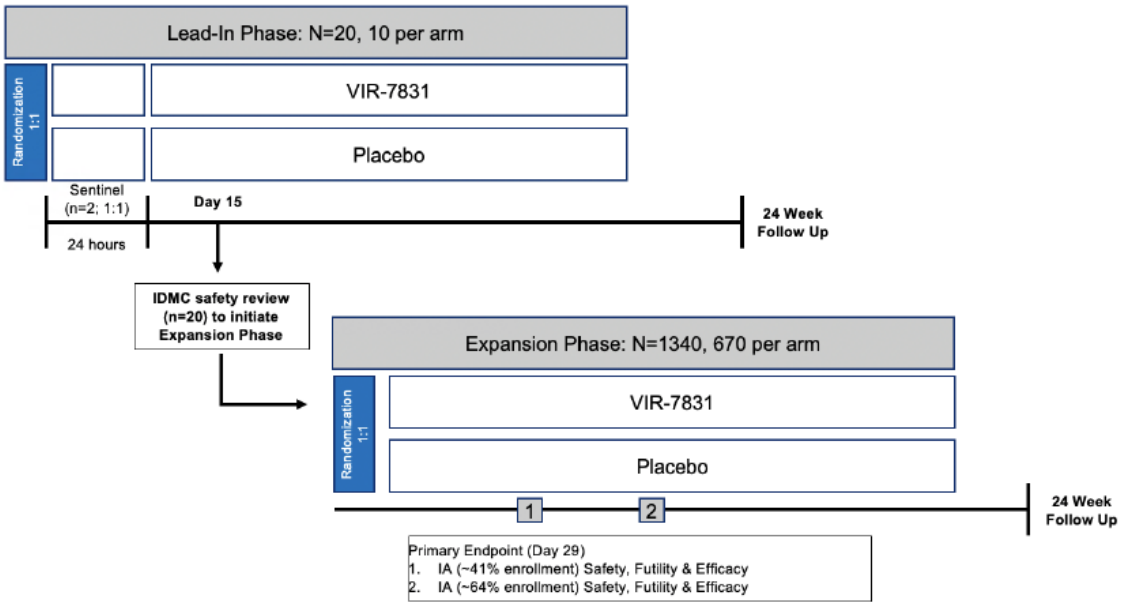
In May 2021, EMA issued advice on use of sotrovimab for treating COVID-19 based on the interim analysis on the first 583 subjects in an article 5(3) procedure.

COMET-ICE study

Methods

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.

Figure 9: Study design schematic



- **Study Participants**

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).

Subjects of 55 years and above could be included irrespective of risk factors.

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.

- **Treatments**

Treatment with sotrovimab was a single infusion of 500 mg during 1 hour. Sotrovimab and placebo (sterile 0.9% (w/v) sodium chloride solution) were administered as the same volume. Participants were observed for 2 hours post treatment.

Medication considered standard of care for COVID-19 was permitted, besides for convalescent plasma and anti-SARS-CoV-2 mAb. Furthermore, hydroxychloroquine and chloroquine were not permitted.

- **Objectives**

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

- **Outcomes/endpoints**

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

- **Sample size**

Approximately 1360 (680 per arm) participants were randomly assigned to study intervention. A total sample size of 1360 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 VIR-7831 arm, respectively. The minimal detectable efficacy for this design at the final efficacy analysis was approximately 25% if disease progression rates is 16% in the placebo arm.

- **Randomisation and blinding (masking)**

The randomisation was stratified by age and symptom duration. In the CHMP advice, it was mentioned that stratification by region was advisable if pre-defined and adequately chosen. The Applicant further stratified the randomisation by region (Europe, North America and South America).

The study was double blinded. Due to the interim analysis, stop due to efficacy and application of temporary authorisation, 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.

- **Statistical methods**

Population: For the primary endpoint, both the ITT population and PP population were used. For the secondary endpoints, the ITT population was used.

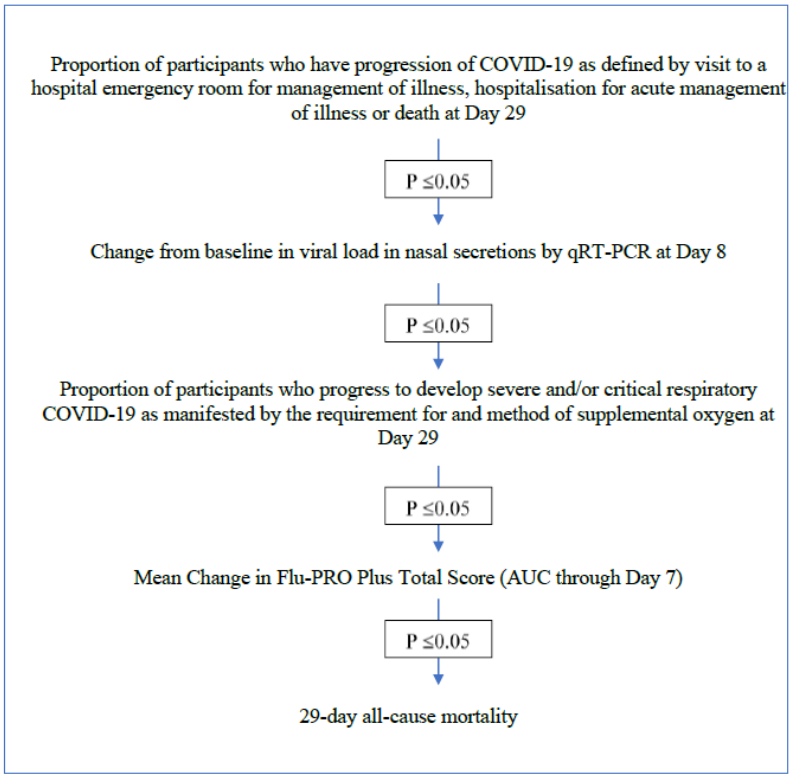
Covariates: The analyses were adjusted for stratification factors (age and duration of symptoms) and gender. Some of the secondary analyses were additionally adjusted for region. Gender was added to

the SAP as an amendment due to increasing importance of gender as a prognostic factor for progression.

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 address 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 and the Applicant has accounted for multiplicity by using hierarchical testing with a two-sided alpha of 0.05 (**Figure 10**). Missing values were imputed using a multiple imputation model or last observation carried forward.

Figure 10: Secondary endpoints testing hierarchy



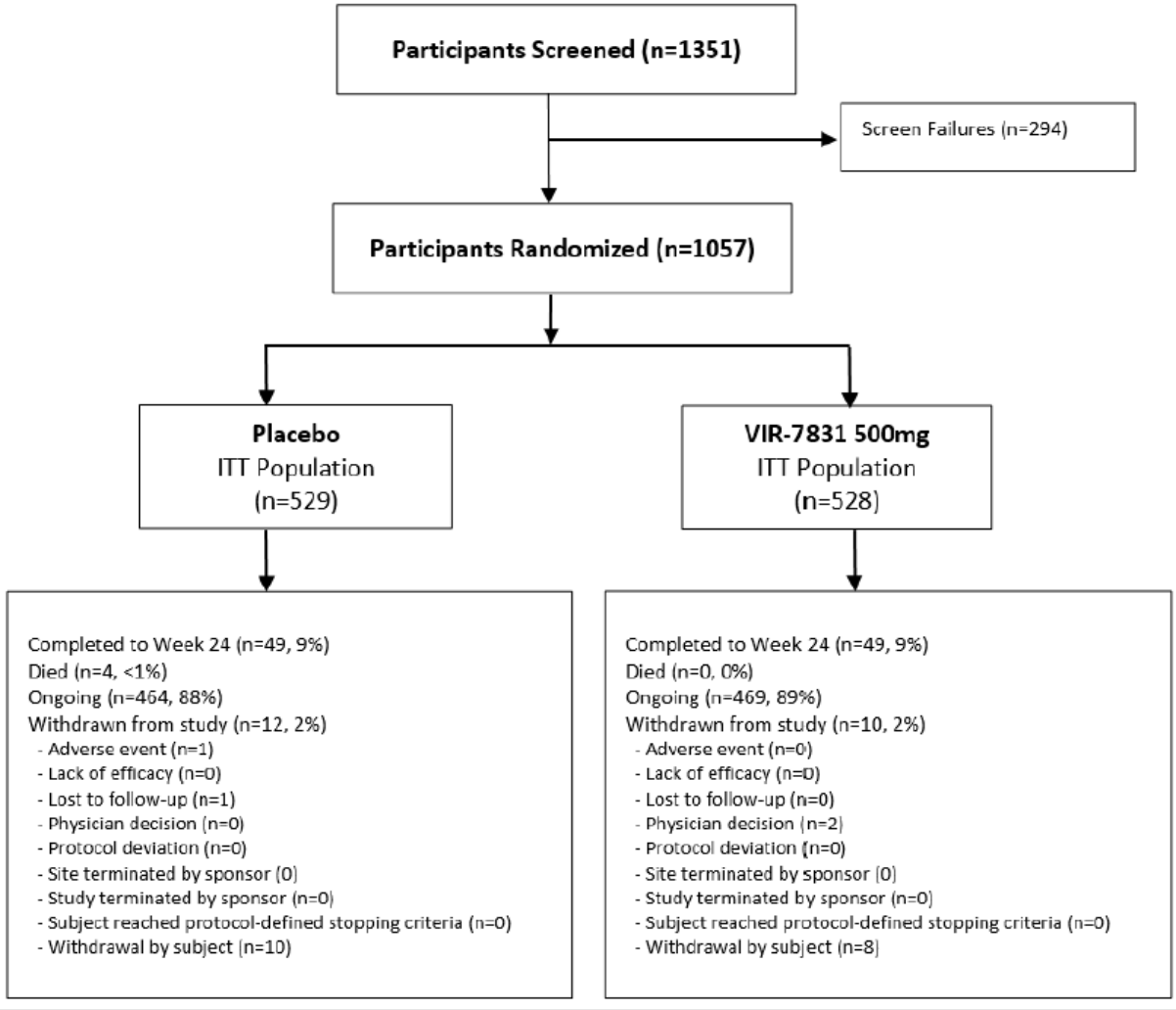
Interim analysis: Two interim analyses were planned when approximately 41% and 64% of the required number of participants have reached Day 29 visit. A Lan-DeMets alpha-spending function to control the type I error for the primary endpoint was used, using a Pocock analogue rule for futility and Hwang-Shih-DeCani (γ = 1) analogue rule for efficacy.

Results

- **Participant flow**

Participant flow is shown in ***Figure 11*** below.

Figure 11: Participant Disposition Through Day 29 (ITT [Day 29])



- **Recruitment and conduct of the study**

This study was conducted at 57 centres total: 45 centres in the USA, 6 in Brazil, 3 in Spain, 2 in Canada, and 1 in Peru. The first participant was enrolled on 27 August 2020 and the last participant completed their Day 29 visit on 08 April 2021 (Day 29 Analysis).

An Independent Data Monitoring Committee (IDMC) actively monitored interim unblinded safety (Lead-in Phase) and interim unblinded safety and efficacy data (Expansion Phase) to make recommendations.

One protocol amendment was implemented the 20th of December 2020. According to the protocol amendment, secondary objectives, secondary endpoints, inclusion and exclusion criteria, interim analysis and safety measures were changed. This amendment was issued after inclusion of the first patient and before completion of patient enrolment and before the interim analysis was conducted at the 4th of March 2021.

- **Baseline data**

Demographics

The baseline demographics characteristics were overall equally distributed across treatment arms (**Table 9**). A marginally higher proportion of women was included in the sotrovimab arm (57%) compared to the placebo arm (52%). The median age was 54 years with a range from 17 to 96 years.

11% of the population was 70 years or above and 20% was above the age of 65 years. Median BMI (range) was 31.8 kg/m2 (17.0-71.2), hence, more than 50% of the population was obese.

Table 9: 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)

Day 29 analysis DCO: 27 April 2021
Source: Table 1.10, Table 1.23.

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

Diagnosis

The majority of patients were diagnosed with SARS-CoV-2 by nasopharyngeal swab and 85% of the method of diagnosis was RT-PCR (Table 10). Viral load was not detectable in 13% of subjects and was below the lower limit of quantification in 7% of subjects. The viral quantification was above log10^7 for 36% of the subjects. Changes in viral load (secondary endpoint) can therefore not be evaluated for 20% of the study population.

Table 10: 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]	470	451	921
Mean (SD)	5.915 (2.0945)	5.824 (2.0392)	5.87 (2.0669)
Median (Min, Max)	6.073 (2.873, 9.941)	6.039 (2.873, 9.985)	6.064 (2.873, 9.985)
Not Detectable	63 (13%)	60 (13%)	123 (13%)
<Lower limit of quantification (<2228 copies/mL)	32 (7%)	33 (7%)	65 (7%)
≤log 10^5	83 (18%)	68 (15%)	151 (16%)
>log 10^5 – ≤log 10^6	55 (12%)	63 (14%)	118 (13%)
>log 10^6 – ≤log 10^7	58 (12%)	71 (16%)	129 (14%)
>log 10^7	179 (38%)	156 (35%)	335 (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

Comorbidities

More than 99% of patients had at least one of the protocol-defined risk factors for progression of COVID-19 (Table 11). About half had only one risk factor and about 30% had two. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%) and asthma (17%). The comorbidities were equally distributed across treatment groups.

Symptoms

The most common COVID-19-related symptoms at baseline are shown below in **Table 11**. The majority was enrolled within 3 days of symptom onset.

Table 11: Summary of risk factors for COVID-19 progression and COVID-19 symptoms (ITT)

Parameter	Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)	Total (N = 1057)
Conditions as risk factor for COVID-19 progression[a]			
Any Condition	526 (>99%)	525 (>99%)	1051 (>99%)
Obesity (BMI >30 kg/m²)[a]	341 (64%)	330 (63%)	671 (63%)
Aged ≥55 (years)	256 (48%)	243 (46%)	499 (47%)
Diabetes requiring medication	109 (21%)	119 (23%)	228 (22%)
Moderate to severe asthma	88 (17%)	90 (17%)	178 (17%)
COPD	27 (5%)	34 (6%)	61 (6%)
Chronic kidney disease (eGFR <60 by MDRD)	8 (2%)	5 (<1%)	13 (1%)
Congestive heart failure (NYHA class II or more)	3 (<1%)	4 (<1%)	7 (<1%)
Number of conditions met [a]			
0[b]	3 (<1%)	3 (<1%)	6 (<1%)
1	304 (57%)	290 (55%)	594 (56%)
2	153 (29%)	178 (34%)	331 (31%)
3	55 (10%)	50 (9%)	105 (10%)
>3	14 (3%)	7 (1%)	21 (2%)
Symptoms present			
Cough	432 (82%)	423 (80%)	855 (81%)
Headache	380 (72%)	373 (71%)	753 (71%)
Muscle aches/myalgia	376 (71%)	373 (71%)	749 (71%)
Fatigue	319 (60%)	329 (62%)	648 (61%)
Malaise	294 (56%)	299 (57%)	593 (56%)
Sore throat	293 (55%)	299 (57%)	592 (56%)
Fever	286 (54%)	281 (53%)	567 (54%)
Loss of taste	283 (53%)	282 (53%)	565 (53%)
Loss of smell	274 (52%)	282 (53%)	556 (53%)
Joint pain/arthralgia	272 (51%)	278 (53%)	550 (52%)
Chills	264 (50%)	279 (53%)	543 (51%)
Shortness of breath	220 (42%)	214 (41%)	434 (41%)
Diarrhoea	179 (34%)	164 (31%)	343 (32%)
Nausea	142 (27%)	159 (30%)	301 (28%)
Vomiting	60 (11%)	60 (11%)	120 (11%)
Symptom duration (days)			
≤3	310 (59%)	314 (59%)	624 (59%)
4-5	219 (41%)	213 (40%)	432 (41%)
>5	0	1 (<1%)	1 (<1%)

Day 29 Analysis DCO: 27 April 2021

Source: Table 1.16.

a. Medical Conditions present at Screening as risk factors for progression included: diabetes (requiring medication), obesity (BMI was amended under protocol amendment 1 from >30 kg/m² to >35 kg/m². Participants are only summarised in the BMI threshold under which they were screened), chronic kidney disease (i.e., estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m² by Modification of Diet in Renal Disease [MDRD]), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion), and moderate-to-severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

b. These were included as protocol deviations; however, none of the participants met the clinical progression endpoints.

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

Prior and concomitant medication

3 subjects in the placebo arm and 2 subjects in the sotrovimab arm received convalescent plasma after COVID-19 progression, and 2 subjects in the placebo arm and 4 subjects in the sotrovimab arm received concomitant hydroxychloroquine.

Remdesivir was also administered to patients who progressed (6 patients in placebo group and 1 patient in the sotrovimab group).

Steroids were used in 7% of subjects in the placebo arm and in 5% of subjects in the sotrovimab arm.

During the 28 days follow-up, the initiation of steroids was more frequent in the placebo group than in the sotrovimab group, e.g. 13 out of 529 subjects in the placebo group vs 2 out of 528 subjects in the

sotrovimab group were treated with IV steroids from day 1 to day 29. Intensification of steroid use during follow-up was not recorded.

- **Numbers analysed**

Summary of disposition of subjects are shown in **Table 12**. A total of 1351 subjects were screened, and of those, 1057 subjects were included in the study and randomised 1:1 to sotrovimab or placebo. 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.

Table 12: 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.

The intention to treat population comprised 1057 subjects and the PP population 1015 subjects (**Table 13**). The number of subjects with virology data at time of submission was 733.

Table 13: 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.

In a supplementary analysis, the PP population should have been used, but due to a low number lost to follow-up, this analysis was omitted.

Protocol deviations

Several protocol deviations were present. Overall, the protocol deviations were equally distributed between sotrovimab and placebo. At randomisation 299 subjects (28%) were mis-stratified. This is mainly attributed to miscalculation of the duration of symptoms, relative to the date of screening. The mis-stratification is similar in both groups and in the analysis, the stratification factor was based on the eCRF and not the assignment at randomisation.

- **Outcomes and estimation**

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% (Table 14).

Primary endpoint, primary analysis

In the placebo group 30 out of 529 subjects and in the sotrovimab group 6 out of 528 subjects 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% (**Table 14**).

No subjects in the sotrovimab group died, whereas 2 subjects in the placebo group died. According to the Applicant, one subject died due to COVID-19 pneumonia and one subject died due to pneumonia.

The risk difference was 6%.

Table 14: Summary of Primary Endpoint Analyses (ITT (IA) 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.

Three of six sotrovimab patients who met the primary endpoint were hospitalised due to COVID-19:

- patient with diabetes, hypertension, hyperlipidaemia and cardiac pacemaker developed Grade 3 COVID-19 on study Day 19 that resolved by study Day 31.
- patient with diabetes, obesity, hypertension and hyperlipidaemia developed Grade 3 COVID-19 pneumonia on study Day 2 that resolved by study day 17.
- patient with diabetes and hypertension developed grade 3 COVID-19 on day 2. He was hospitalised for 5 days and received oxygen by simple facemask for 3 days.

The three others were hospitalised for non-COVID-19 reasons:

- patient with diabetes, BMI >35, asthma, COPD, congestive heart failure, hypertension, hyperlipidaemia, stroke and recent small bowel obstruction developed Grade 2 small bowel obstruction on study Day 22, which resolved by study Day 24.
- patient with diabetes, CCF, COPD and obesity developed a diabetic ulcer on day 17 requiring hospitalisation. He did not receive oxygen.
- patient with diabetes and obesity developed grade 3 NSC lung cancer on day 13 and was hospitalised for 11 days but did not receive oxygen.

Primary endpoint, sensitivity analysis

In a sensitivity analysis, where missing values (5 in placebo and 7 in sotrovimab) were imputed as events (treatment failures), the relative risk ratio was 0.38 (95% CI: 0.20;0.70) and the corresponding relative risk reduction was 62% (**Table 15**).

Table 15: Summary and Analysis of Proportion of Participants who Have Progression of COVID-19 Through Day 29 (Hospitalisation for >24 Hours or Death): Missing Progression Status Considered as Progression (ITT [IA] 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 Status, n (%)				
Hospitalised >24 hours or Death, due to any cause	22 (8%)	7 (2%)	35 (7%)	13 (2%)
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%)	0
Alive and not hospitalised	270 (92%)	284 (98%)	494 (93%)	515 (98%)
Missing[a, b]	1 (<1%)	4 (1%)	5 (<1%)	7 (1%)
Sotrovimab 500 mg vs. Placebo				
Adjusted Relative Risk Ratio	0.32		0.38	
97.24% Confidence Interval	0.12, 0.81		0.19, 0.76	
95% CI	0.14, 0.73		0.20, 0.70	
p-value	0.007		0.003	
Risk difference	-6.38		-5.55	

Interim Analysis 1 DCO: 04 March 2021
Day 29 Analysis DCO: 27 April 2021
Source: Table 2.51 and Table 2.8

a. For ITT (IA): Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to dosing and 4 sotrovimab participants (4 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons Note: Relative risk ratio is presented using a Poisson regression model with a robust sandwich estimator, adjusted for treatment (sotrovimab vs. placebo), duration of symptoms (≤3 days vs.≥4 days), age ≤70 vs. >70 years old) and gender (female vs. male) as covariates. Available data were used in the analysis as collected, regardless of the occurrence of intercurrent events. Missing data were imputed as a progression (treatment failure). Participants are counted in each subcategory of progression experienced up to the time point in question so may be included in more than one category

b. 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 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).

When comparing tables 14 and 15, there were 7 patients randomised to sotrovimab with missing data who were counted as meeting the primary endpoint in Table 15. Four of these 7 patients decided to withdraw before receiving sotrovimab and 2 were withdrawn by the investigator before receiving sotrovimab. The remaining patient received sotrovimab but withdrew for personal reasons on day 5.

Secondary endpoints

Summary of secondary endpoints in the test hierarchy is provided in **Table 16**. Overall, the 5 secondary endpoints were statistically significant. Details of some of the secondary endpoints are provided below.

Table 16: Summary of Secondary Endpoint Testing Hierarchy

Secondary Endpoint	Placebo (N = 529)	Sotrovimab (500 mg IV) (N = 528)
Proportion of participants with Progression of COVID-19 (Hospitalisation or ER visit or Death) through Day 29 (ITT [Day 29])		
Relative Risk Ratio	0.34	
95% CI	0.19, 0.63	
p-value	<0.001	
Change from Baseline in Viral Load in Nasal Secretions by qRT-PCR at Day 8 (Virology)		
n[a]	305	294
LS Mean Difference (SE)	-0.232 (0.0851)	
95% CI	-0.399, -0.065	
p-value	0.007	
Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 through Day 29 (ITT [Day 29])		
Relative Risk Ratio	0.26	
95% CI	0.12, 0.59	
p-value	0.002	
Mean Change from baseline of COVID-19 related illness as measured by FLU-PRO Plus (Total Score, AUC through Day 7) (ITT [Day 29])		
n[b]	399	412
LS Mean Difference (SE)	-1.07 (0.158)	
95% CI	-1.38, -0.76	
p-value	<0.001	
All-Cause Mortality at Day 29 (ITT [Day 29])[c]		
Deceased (n, %)	2 (<1%)	0

Day 29 Analysis DCO 27 April 2021
Source: Table 2.13

a. Number of participants with analysable data at Day 8.
b. Number of participants included in the analysis.
c. Log-rank test was not performed due to insufficient number of events.

For the secondary endpoint including **ER visit, hospitalisation of any duration or death**, the relative risk ratio was 0.34 (95% CI: 0.19;0.63, p<0.001). Among the hospitalised patients, 19/29 subjects in the placebo group and 3/7 subjects in the sotrovimab group were hospitalised due to COVID-19 pneumonia (**Table 17**). Three of the other four in the sotrovimab group are described above and one was hospitalised for <24 h so was not counted in the primary endpoint analysis.

Table 17: Summary of Reasons for Hospitalisation of Any Duration (ITT (Day 29))

	Placebo (N=526)	Sotrovimab (500 mg IV) (N=523)
Number of Participants Hospitalised	29 (6%)	7 (1%)
Reason for Hospitalisation (SAE preferred term)		
COVID-19	2 (<1%)	0
COVID-19 pneumonia[a, b]	19 (4%)	3 (<1%)
Small intestinal obstruction	0	1 (<1%)
Diabetes mellitus[c]	0	1 (<1%)
Acute respiratory failure	1 (<1%)	0
Dehydration	1 (<1%)	0
Hypovolaemia[a]	1 (<1%)	0
Pneumonia	3 (<1%)	0
Pulmonary embolism	1 (<1%)	0
Respiratory distress	2 (<1%)	0
Respiratory failure[d]	1 (<1%)	0
Acute kidney injury[b, d]	2 (<1%)	0
Cardio-respiratory arrest[d]	1 (<1%)	0
Non-small lung cancer	0	1 (<1%)
Diabetic foot	0	1 (<1%)

Day 29 analysis DCO: 27 April 2021.
Source: Listing 16 and Listing 17

a. One participant reported hypovolaemia and COVID-19 pneumonia
b. One participant reported COVID-19 pneumonia and acute kidney injury
c. One participant reported diabetes mellitus and was hospitalised for <24 hours.
d. One participant reported respiratory failure, cardio-respiratory arrest and acute kidney injury

Note: This table is based on the SAEs resulting in progression to hospitalisation (any duration) through Day 29. Only the first hospitalisation for any individual participant is included.

Among those who were hospitalised (exploratory endpoint), the duration of stay was shorter in the sotrovimab group (**Table 18**).

Table 18: Summary of Duration in Hospital from Randomisation through Day 29 (ITT)

	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)
Alive and never entered Hospital[a]	494 (93%)	515 (98%)
Entered Hospital, n (%)	29 (5%)	7 (1%)
1 stay	29 (5%)	7 (1%)
2 stays	0	0
>2 stays	0	0
Incomplete follow-up due to study withdrawal[b]	9 (2%)	7 (1%)
Entered Hospital prior to study withdrawal	4 (<1%)	1 (<1%)
Withdrawal and never entered Hospital	5 (<1%)	6 (1%)
Incomplete follow-up due to death	2 (<1%)	0
Entered Hospital prior to death	1 (<1%)	0
Deceased and never entered Hospital	1 (<1%)	0
Hospital stay, n (%)		
0 days	499 (94%)	521 (99%)
>0 - ≤ 24 hours	0	1 (<1%)
1 to ≤8 days	19 (4%)	3 (<1%)
9 to ≤15 days	3 (<1%)	2 (<1%)
16 to ≤22 days	4 (<1%)	1 (<1%)
23 to ≤29 days	4 (<1%)	0

Day 29 analysis DCO 27 April 2021
Source: Table 2.37

a. Alive and no hospital stays based on complete follow-up data
b. 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

For progression to severe and/or critical COVID-19, 28 subjects in the placebo group and 7 subjects in the sotrovimab group **required oxygen supplementation** during 29 days follow-up (Table 19). The relative risk ratio was 0.26 (95% CI: 0.12;0.59) corresponding to a relative risk reduction of 74% (95% CI: 41%, 88%). No subjects in the sotrovimab group required non-rebreather mask, high flow oxygen or mechanical ventilation, whereas this was the case in the placebo group for 14 subjects.

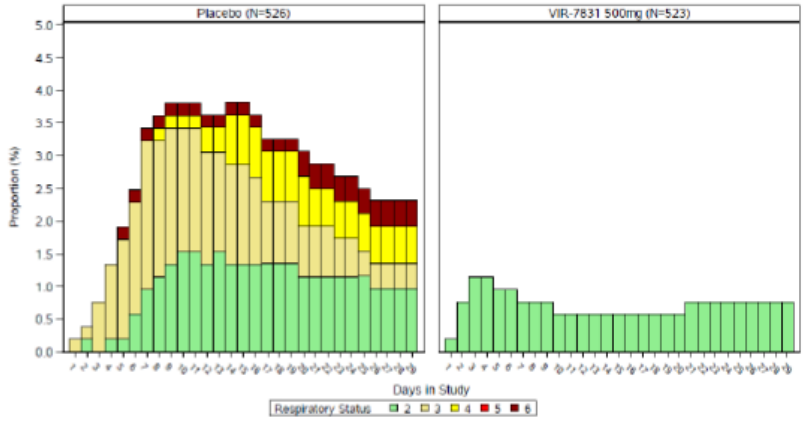
An overview of the daily proportion of participants in 5 of the 6 respiratory support categories over 29 days is shown in **Figure 12**.

Table 19: 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 [Day 29])

	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 2.26
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.

Figure 12: Stacked Bar Chart of Respiratory Status over time excluding room air



Note: Respiratory Support Status Categories defined as: 1= Room Air, 2= Low flow nasal cannulae/face mask, 3= Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support), 4= Mechanical ventilation/extra-corporeal membrane oxygenation, 5= Other, 6= Death.
Source: m5.3.5.1, COMET-ICE CSR, Figure 3.8

The mean change in **viral load** at day 8 was larger in the sotrovimab group than the placebo group (**Table 20**). When the analysis was stratified by baseline viral load, there was a tendency of a higher effect in subjects with the highest viral load and no effect in those with the lowest viral load.

Table 20: Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)

	Placebo (N=385)	Sotrovimab (500 mg IV) (N=369)
Baseline (log 10 copies/mL)		
n	385	369
Mean (standard deviation)	6.645 (1.6632)	6.535 (1.6331)
Day 8 viral load (log 10 copies/mL)		
n	323	316
Mean (standard deviation)	4.276 (1.3646)	3.989 (1.1913)
Day 8 change from baseline (log 10 copies/mL) [a]		
LS Mean Change from Baseline (SE)	-2.358 (0.0589)	-2.610 (0.0593)
95% CI	(-2.474, -2.243)	(-2.726, -2.493)
Difference (SE)	-0.251 (0.0835)	
95% CI	(-0.415, -0.087)	
p-value	0.003	

The mean change in **FLU-PRO Plus total score** (AUC through day 7) was calculated from available completed questionnaires (~80% day 1, ~50% day 21). The mean decreases in total score were statistically significantly greater for sotrovimab vs. placebo based on AUC0-7, 0-14 and 0-21.

Table 21: 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, and 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
Source: Table 4.2.

The probability of reaching **sustained symptom resolution** was statistically significantly greater for sotrovimab vs. placebo (**Table 22**).

Table 22: 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.

Up to day 29, no **deaths** occurred in the sotrovimab group vs. 2 in the placebo group among those with data. Details of censored patients are provided in the footnote in **Table 23** below.

Table 23: 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.

- **Ancillary analyses**

Predefined subgroup analyses

Subgroup analysis by age (≤70, >70 years)

Interpretation of results for the primary endpoint by age randomisation strata requires caution due to limited number of patients. There are 56 patients per treatment group in the older stratum (70+ years).

Numerically larger effect on the primary endpoint among subjects ≤ 70 years were seen compared with subjects >70 years (***Table 24***). As such, the relative risk ratio was 0.18 (95% CI: 0.06;0.52) in subjects ≤ 70 years and 0.31 (95% CI: 0.07;1.41) in subjects > 70 years and were generally consistent with those for the overall ITT day 29 population. A similar conclusion applied to analyses of secondary endpoints by age strata.

Table 24: Summary of Primary and Key Secondary Efficacy Endpoints by Randomised Age Group (≤70, >70 Years)

Age	≤70 years		>70 years	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	473	472	56	56
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	23 (5%)	4 (<1%)	7 (13%)	2 (4%)
Hospitalised >24 hours for acute management of any illness	23 (5%)	4 (<1%)	6 (11%)	2 (4%)
Death due to any cause	1 (<1%)	0	1 (2%)	0
Alive and not hospitalised >24 hours	445 (94%)	462 (98%)	49 (88%)	53 (95%)
Missing[a]	5 (1%)	6 (1%)	0	1 (2%)
Relative risk ratio	0.18		0.31	
95% CI	0.06, 0.52		0.07, 1.41	
Risk difference	-4.00		-8.70	
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT [Day 29])				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	31 (7%)	11 (2%)	8 (14%)	2 (4%)
Hospitalised for acute management of any illness, any duration	23 (5%)	5 (1%)	6 (11%)	2 (4%)
ER visit due to any cause	9 (2%)	6 (1%)	1 (2%)	0
Death due to any cause	1 (<1%)	0	1 (2%)	0
Alive and not hospitalised and no ER visit	437 (92%)	455 (96%)	48 (86%)	53 (95%)
Missing[a]	5 (1%)	6 (1%)	0	1 (2%)
Relative risk ratio	0.36		0.26	
95% CI	0.18, 0.71		0.06, 1.18	
Risk difference	-4.27		-10.82	
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT [Day 29])				
Progression Status, n (%)				
No Severe/Critical Progression[c]	446 (94%)	461 (98%)	49 (88%)	53 (95%)
Severe/Critical Progression[d]	21 (4%)	5 (1%)	7 (13%)	2 (4%)

Category 2: Low flow nasal cannulae/face mask (severe)	9 (2%)	5 (1%)	3 (5%)	2 (4%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	9 (2%)	0	1 (2%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	2 (<1%)	0	2 (4%)	0
Death	1 (<1%)	0	1 (2%)	0
Missing[e]	6 (1%)	6 (1%)	0	1 (2%)
Relative risk ratio	0.25		0.30	
95% CI	0.09, 0.65		0.07, 1.40	
Risk difference	-3.41		-8.88	
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n [f]	267	258	38	36
LS mean change from baseline (standard error)	-2.468 (0.0634)	-2.633 (0.0642)	-1.546 (0.1696)	-2.252 (0.1754)
95% CI	-2.593, -2.344	-2.759, -2.507	-1.879, -1.213	-2.597, -1.908
Difference (standard error)	-0.165 (0.0903)		-0.706 (0.2436)	
95% CI	-0.342, 0.012		-1.184, -0.227	

Day 29 analysis DCO: 27 April 2021.
Source: Table 2.10, Table 2.15, Table 2.27 and Table 2.20

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8

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

Subgroup analysis by duration of symptoms

No differences in the primary endpoint were seen between groups with duration of symptoms ≤3 days and ≥ 4 days (**Table 25**). Additionally, no differences in efficacy were seen in the secondary endpoint of severe / critical respiratory COVID-19 between the two groups.

Table 25: Summary of Primary and Key Secondary Efficacy Endpoints by Duration of Symptoms (≤3 days, ≥4 days)

Duration of Symptoms	**≤3 days**		**≥4 days**	
	Placebo	**Sotrovimab (500 mg IV)**	**Placebo**	**Sotrovimab (500 mg IV)**
Number of Participants	310	314	219	214
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	17 (5%)	3 (<1%)	13 (6%)	3 (1%)
Hospitalised >24 hours for acute management of any illness	16 (5%)	3 (<1%)	13 (6%)	3 (1%)
Death due to any cause	1 (<1%)	0	1 (<1%)	0
Alive and not hospitalised >24 hours	290 (94%)	309 (98%)	204 (93%)	206 (96%)
Missing[a]	3 (<1%)	2 (<1%)	2 (<1%)	5 (2%)
Relative risk ratio	0.18		0.25	
95% CI	0.05, 0.62		0.07, 0.84	
Risk difference	-6.09		-6.48	
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT) (Day 29)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	22 (7%)	6 (2%)	17 (8%)	7 (3%)
Hospitalised for acute management of any illness, any duration	16 (5%)	4 (1%)	13 (6%)	3 (1%)
ER visit due to any cause	6 (2%)	2 (<1%)	4 (2%)	4 (2%)
Death due to any cause	1 (<1%)	0	1 (<1%)	0
Alive and not hospitalised and no ER visit	285 (95%)	306 (97%)	200 (91%)	202 (94%)
Missing[a]	3 (<1%)	2 (<1%)	2 (<1%)	5 (2%)
Relative risk ratio	0.27		0.43	
95% CI	0.11, 0.67		0.18, 1.02	
Risk difference	-6.59		-5.81	
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT) (Day 29)				
Progression Status, n (%)				
No Severe/Critical Progression[c]	290 (94%)	309 (98%)	205 (94%)	205 (96%)
Severe/Critical Progression[d]	16 (5%)	3 (<1%)	12 (5%)	4 (2%)

Duration of Symptoms	≤3 days		≥4 days	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Category 2: Low flow nasal cannulae/face mask (severe)	9 (3%)	3 (<1%)	3 (1%)	4 (2%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	4 (1%)	0	6 (3%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	2 (<1%)	0	2 (<1%)	0
Death	1 (<1%)	0	1 (<1%)	0
Missing[e]	4 (1%)	2 (<1%)	2 (<1%)	5 (2%)
Relative risk ratio	0.19		0.35	
95% CI	0.06, 0.65		0.12, 1.07	
Risk difference	-5.83		-5.21	
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n[f]	177	177	128	117
LS mean change from baseline (standard error)	-2.364 (0.0790)	-2.613 (0.0788)	-2.345 (0.0921)	-2.556 (0.0965)
95% CI	-2.519, -2.209	-2.768, -2.458	-2.526, -2.164	-2.745, -2.367
Difference (standard error)	-0.249 (0.1112)		-0.211 (0.1331)	
95% CI	-0.467, -0.030		-0.472, 0.051	

Duration of Symptoms	≤3 days		≥4 days	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)

Day 29 analysis DCO: 27 April 2021
Source: Table 2.11, Table 2.16, Table 2.28 and Table 2.21

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8

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

Subgroup analysis by region

The proportion of subjects in the placebo group with hospitalisation >24 hours or death was highest in South America (42%) and lowest in North America (5%) (**Table 26**). Although small numbers, the treatment effect was largest in South America and smallest in North America.

Table 26: Summary of Primary and Key Secondary Efficacy Endpoints by Region

Region	North America		Europe		South America	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	502	503	15	14	12	11
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	23 (5%)	6 (1%)	2 (13%)	0	5 (42%)	**0**
Hospitalised >24 hours for acute management of any illness[b]	22 (4%)	6 (1%)	2 (13%)	0	5 (42%)	0
Death due to any cause	2 (<1%)	0	0	0	0	0
Alive and not hospitalised >24 hours	474 (94%)	491 (98%)	13 (87%)	13 (93%)	7 (58%)	11 (100%)
Missing[a]	5 (<1%)	6 (1%)	0	1 (7%)	0	0
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT) (Day 29)						
Progression Status, n (%)						
No Severe/Critical Progression[c]	475 (95%)	490 (97%)	13 (87%)	13 (93%)	7 (58%)	11 (100%)
Severe/Critical Progression[d]	21 (4%)	7 (1%)	2 (13%)	0	5 (42%)	0
Category 2: Low flow nasal cannulae/face mask (severe)	10 (2%)	7 (1%)	1 (7%)	0	1 (8%)	0
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	7 (1%)	0	1 (7%)	0	2 (17%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	2 (<1%)	0	0	0	2 (17%)	0
Death	2 (<1%)	0	0	0	0	0
Missing[e]	6 (1%)	6 (1%)	0	1 (7%)	0	0

Region	North America		Europe		South America	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)						
n[f]	287	272	11	13	7	9
LS mean change from baseline (standard error)	-2.393 (0.0615)	-2.621 (0.0628)	-1.601 (0.3233)	-2.004 (0.3017)	-2.038 (0.3931)	-2.382 (0.3605)
95% CI	-2.513, -2.272	-2.744, -2.497	2.236, -0.967	-2.596, -1.411	-2.809, -1.266	-3.090, -1.674
Difference (standard error)		-0.228 (0.0879)	-0.402 (0.4392)		-0.345 (0.5315)	
95% CI		-0.401, -0.055	-1.265, 0.460		-1.388, 0.699	
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT) (Day 29)						
Region[g]	**US**				**Non-US**	
Progression Status, n (%)	**Placebo (N=474)**	**Sotrovimab (500 mg IV) (N=479)**			**Placebo (N=55)**	**Sotrovimab (500 mg IV) (N=49)**
Hospitalised, ER visit or Death, due to any cause	29 (6%)	11 (2%)			10 (18%)	2 (4%)
Hospitalised for acute management of any illness, any duration	21 (4%)	7 (1%)			8 (15%)	0
ER visit due to any cause	8 (2%)	4 (<1%)			2 (4%)	2 (4%)
Death due to any cause	2 (<1%)	0			0	0
Alive and not hospitalised and no ER visit	440 (93%)	462 (96%)			45 (82%)	46 (94%)
Missing[e]	5 (1%)	6 (1%)			0	1 (2%)
Relative risk ratio	0.38				0.24	
95% CI	0.19, 0.75				0.05, 1.04	
Risk difference	-4.87				-16.35	
Day 29 Analysis DCO: 27 April 2021. Source: m5.3.5.1, COMET-ICE CSR, Table 2.12, Table 2.17, Table 2.29 and Table 2.22						

Region	North America		Europe		South America	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8
g. For the secondary endpoint of hospitalisation or ER visit or death, the model investigating region subgroup did not converge; to assess any geographical difference, region was grouped as US and non-US only.

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

Subgroup analyses by predefined risk-factors for progression

Age (<55, ≥55)

The results for the primary and secondary endpoints by age <55/>55 years were generally consistent with those reported in the overall population. There was a slightly higher rate of disease progression in the older subset in both treatment arms. All patients that met the primary endpoint in the sotrovimab arm were aged at least 55 years.

Table 27: Summary of Primary and Key Secondary Efficacy Endpoints by Age Risk Factor (<55 years,≥55 years)

	<55years		≥55 years	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	273	285	256	243
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death) (ITT) (Day 29) [g]				
Progression Status, n (%)				
Hospitalised >24 hours or Death, due to any cause	6 (2%)	0	24 (9%)	6 (2%)
Hospitalised >24 hours for acute management of any illness	6 (2%)	0	24 (9%)	6 (2%)
Death due to any cause	0	0	2 (<1%)	0
Alive and not hospitalised >24 hours	265 (97%)	280 (98%)	229 (89%)	235 (97%)
Missing[a]	2 (<1%)	5 (2%)	3 (1%)	2 (<1%)
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT) (Day 29)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	12 (4%)	4 (1%)	27 (11%)	9 (4%)
Hospitalised for acute management of any illness, any duration	6 (2%)	1 (<1%)	23 (9%)	6 (2%)
ER visit due to any cause	6 (2%)	3 (1%)	4 (2%)	3 (1%)
Death due to any cause	0	0	2 (<1%)	0
Alive and not hospitalised and no ER visit	259 (95%)	276 (97%)	226 (88%)	232 (95%)
Missing[a]	2 (<1%)	5 (2%)	3 (1%)	2 (<1%)
Relative risk ratio	0.33	0.36		
95% CI	0.11, 1.02	0.17, 0.75		
Risk difference	-3.00	-6.88		
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT) (Day 29)				
Progression Status, n (%)				
No Severe/Critical Progression[c]	264 (97%)	279 (98%)	231 (90%)	235 (97%)
Severe/Critical Progression[d]	7 (3%)	1 (<1%)	21 (8%)	6 (2%)
Category 2: Low flow nasal cannulae/face mask (severe)	4 (1%)	1 (<1%)	8 (3%)	6 (2%)

	<55years		≥55 years	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	3 (1%)	0	7 (3%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	0	0	4 (2%)	0
Death	0	0	2 (<1%)	0
Missing[e]	2 (<1%)	5 (2%)	4 (2%)	2 (<1%)
Relative risk ratio	0.15		0.31	
95% CI	0.02, 1.21		0.13, 0.75	
Risk difference	-2.21		-5.75	
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n[f]	156	153	149	141
LS mean change from baseline (standard error)	-2.664 (0.0840)	-2.611 (0.0834)	-2.043 (0.0849)	-2.565 (0.0878)
95% CI	-2.829, -2.499	-2.775, -2.448	-2.209, -1.876	-2.738, -2.393
Difference (standard error)	-0.052 (0.1183)		-0.5238 (0.1219)	
95% CI	-0.180, -0.285		-0.762, -0.283	

Day 29 Analysis DCO: 27 April 2021.
Source: m.5.3.5.3, SDAP outputs for efficacy, Table 12.29, Table 12.30 and Table 12.31 and Table 12.32
a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8.
g. Analysis was not performed as the model did not converge.
Note: Participants are counted in each subcategory of progression experienced up to the time point in question and may be included in more than one category.
Note: 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.

Obesity

In the analyses stratified by the pre-defined risk factor, obesity (BMI ≤30 kg/m2, >30 kg/m2), the primary endpoint occurred in 4% in the placebo group and 2% in the sotrovimab group among obese patients and in 10% in the placebo group and <1% in the sotrovimab group in non-obese patients (**Table 28**). The corresponding relative risk ratios were 0.45 (95% CI: 0.16;1.26) in obese subjects and 0.06 (95% CI: 0.01;0.42) in non-obese subjects. The relative risk reduction was therefore smaller and non-statistically significant in obese subjects (55%) than in non-obese subjects (94%). A similar pattern was seen for the respiratory endpoint with a relative risk ratio of 0.47 (95% CI: 0.22; 1.03) in subjects with obesity and 0.21 (95% CI: 0.07; 0.60) in subjects without obesity.

The Applicant has elaborated on those results and has discussed that the effect of BMI may have been confounded by age, as the non-obese subjects on average were older (median age 59 years, 35% >65 years) than the obese subjects (median age 50 years, 12% > 65 years).

Table 28: Summary of Primary and Key Secondary Efficacy Endpoints by Obesity Risk Factor (BMI ≤30 kg/m2, >30 kg/m2)

	BMI ≤30 kg/m²		BMI >30 kg/m²	
	Placebo	**Sotrovimab (500 mg IV)**	**Placebo**	**Sotrovimab (500 mg IV)**
Number of Participants	188	198	341	330
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	18 (10%)	1 (<1%)	12 (4%)	5 (2%)
Hospitalised >24 hours for acute management of any illness	17 (9%)	1 (<1%)	12 (4%)	5 (2%)
Death due to any cause	1 (<1%)	0	1 (<1%)	0
_Alive and not hospitalised >24 hours	169 (90%)	195 (98%)	325 (95%)	320 (97%)
_Missing[a]	1 (<1%)	2 (1%)	4 (1%)	5 (2%)
Relative risk ratio	0.06		0.45	
95% CI	0.01, 0.42		0.16, 1.26	
Risk difference	-10.90		-2.76	
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT) (Day 29)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	19 (10%)	4 (2%)	20 (6%)	9 (3%)
Hospitalised for acute management of any illness, any duration	17 (9%)	2 (1%)	12 (4%)	5 (2%)
ER visit due to any cause	2 (1%)	2 (1%)	8 (2%)	4 (1%)
Death due to any cause	1 (<1%)	0	1 (<1%)	0
_Alive and not hospitalised and no ER visit	168 (89%)	192 (97%)	317 (93%)	316 (96%)
_Missing[a]	1 (<1%)	2 (1%)	4 (1%)	5 (2%)
Relative risk ratio	0.21		0.47	
95% CI	0.07, 0.60		0.22. 1.03	
Risk difference	-9.53		-4.10	
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT) (Day 29)				
Progression Status, n (%)				
No Severe/Critical Progression[c]	170 (90%)	193 (97%)	325 (95%)	321 (97%)
Severe/Critical Progression[d]	16 (9%)	3 (2%)	12 (4%)	4 (1%)

	BMI ≤30 kg/m²		BMI >30 kg/m²	
	Placebo	**Sotrovimab (500 mg IV)**	**Placebo**	**Sotrovimab (500 mg IV)**
Category 2: Low flow nasal cannulae/face mask (severe)	8 (4%)	3 (2%)	4 (1%)	4 (1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	5 (3%)	0	5(1%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	2 (1%)	0	2 (<1%)	0%)
Death	1 (<1%)	0	1 (<1%)	0
Missing[e]	2 (1%)	2 (1%)	4 (1%)	5 (2%)
Relative risk ratio	0.19		0.36	
95% CI	0.06, 0.63		0.12, 1.10	
Risk difference	-8.49		-3.32	
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n[f]	104	106	201	188
LS mean change from baseline (standard error)	-2.182 (0.1022)	-2.663 (0.1014)	-2.450 (0.0739)	-2.547 (0.0758)
95% CI	-2.382, -1.981	-2.863, -2.464	-2.596 (-2.305)	-2.696, -2.398
Difference (standard error)	-0.482 (0.1432)		-0.096 (0.1056)	
95% CI	-0.763, -0.200		-0.304, 0.111	

Day 29 Analysis DCO: 27 April 2021.
Source: m.5.3.5.3, SDAP outputs for efficacy, Table 12.33, Table 12.34, Table 12.35, and Table 12.36

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8.

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

Diabetes Requiring Medication

Subgroup results among those who did and did not have diabetes requiring medication were generally consistent with those reported in the overall population. All the primary endpoint progressions in the sotrovimab arm occurred in participants with diabetes.

Table 29: Summary of Primary and Key Secondary Efficacy Endpoints by Presence of Diabetes Requiring Medication Risk Factor

	No Presence of Diabetes Requiring Medication		Presence of Diabetes Requiring Medication	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	420	409	109	119
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death) (ITT) (Day 29)[g]				
Progression Status, n (%)				
Hospitalised >24 hours or Death, due to any cause	21 (5%)	0	9 (8%)	6 (5%)
Hospitalised >24 hours for acute management of any illness	20 (5%)	0	9 (8%)	6 (5%)
Death due to any cause	2 (<1%)	0	0	0
Alive and not hospitalised >24 hours	395 (94%)	402 (98%)	99 (91%)	113 (95%)
Missing[a]	4 (<1%)	7 (2%)	1 (<1%)	0
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT) (Day 29)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	27 (6%)	6 (1%)	12 (11%)	7 (6%)
Hospitalised for acute management of any illness, any duration	20 (5%)	0	9 (8%)	7 (6%)
ER visit due to any cause	7 (2%)	6 (1%)	3 (3%)	0
Death due to any cause	2 (<1%)	0	0	0
Alive and not hospitalised and no ER visit	389 (93%)	396 (97%)	96 (88%)	112 (94%)
Missing[a]	4 (<1%)	7 (2%)	1 (<1%)	0
Relative risk ratio	0.24		0.54	
95% CI	0.10, 0.57		0.22, 1.31	
Risk difference	-6.40		-6.40	
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT) (Day 29)				
Progression Status, n (%)				
No Severe/Critical Progression[c]	394 (94%)	398 (97%)	101 (93%)	116 (97%)
Severe/Critical Progression[d]	21 (5%)	4 (<1%)	7 (6%)	3 (3%)

	No Presence of Diabetes Requiring Medication		Presence of Diabetes Requiring Medication	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Category 2: Low flow nasal cannulae/face mask (severe)	8 (2%)	4 (<1%)	4 (4%)	3 (3%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	7 (2%)	0	3 (3%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	4 (<1%)	0	0	0
Death	2 (<1%)	0	0	0
Missing[e]	5 (1%)	7 (2%)	1 (<1%)	0
Relative risk ratio	0.21		0.40	
95% CI	0.07, 0.60		0.11, 1.51	
Risk difference	-5.83		-5.18	
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n[f]	241	224	64	60
LS mean change from baseline (standard error)	-2.375 (0.0676)	-2.594 (0.0695)	-2296 (0.1290)	-2.573 (0.1243)
95% CI	-2.507, -2.242	-2.731, -2.457	-2.549, -2.043	-2.817, -2.28
Difference (standard error)	-0.219 (0.0969)		-0.277 (0.1791)	
95% CI	-0.410, -0.029		-0.628, 0.075	

Day 29 Analysis DCO: 27 April 2021.
Source: m.5.3.5.3, SDAP outputs for efficacy, Table 12.37, Table 12.38, Table 12.39 and Table 12.40

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8.
g. Analysis was not performed as the model did not converge.

	No Presence of Diabetes Requiring Medication		Presence of Diabetes Requiring Medication	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)

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

Moderate to Severe Asthma

In the analyses stratified by the pre-defined risk factor, moderate/severe asthma (yes/no), the primary endpoint occurred in 3% in the placebo group and in no subjects in the sotrovimab group among subjects with moderate or severe asthma and in 6% in the placebo group and 1% in the sotrovimab group in subjects without asthma (Appendix **Table 30**). Hence the effect was numerically larger in subjects with asthma than without asthma. A similar pattern was seen for the respiratory endpoint. It is noted that the primary endpoint was more frequent in patients without asthma compared with patients with asthma.

Table 30: Summary of Primary and Key Secondary Efficacy Endpoints by Presence of Moderate to Severe Asthma Risk Factor (Day 29)

	No Presence of Moderate to Severe Asthma		Presence of Moderate to Severe Asthma	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	441	**438**	88	90
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death) (ITT) (Day 29)[g]				
Progression Status, n (%)				
_Hospitalised >24 hours or Death, due to any cause	27 (6%)	6 (1%)	3 (3%)	0
Hospitalised >24 hours for acute management of any illness	26 (6%)	6 (1%)	3 (3%)	0
Death due to any cause	1 (<1%)	0	1 (1%)	0
_Alive and not hospitalised >24 hours	411 (93%)	425 (97%)	83 (94%)	90 (100%)
_Missing[a]	3 (<1%)	7 (2%)	2 (2%)	0
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation or Emergency Room Visit or Death) (ITT) (Day 29)				
Progression Status, n (%)				
Hospitalised, ER visit or Death, due to any cause	36 (8%)	12 (3%)	3 (3%)	1 (1%)
Hospitalised for acute management of any illness, any duration	26 (6%)	7 (2%)	3 (3%)	0
ER visit due to any cause	10 (2%)	5 (1%)	0	1 (1%)
Death due to any cause	1 (<1%)	0	1 (1%)	0
_Alive and not hospitalised and no ER visit	402 (91%)	419 (96%)	83 (94%)	89 (99%)
_Missing[a]	3 (<1%)	7 (2%)	2 (2%)	0
Relative risk ratio	0.35		0.30	
95% CI	0.18, 0.66		0.03, 2.78	
Risk difference	-6.67		-3.51	
Proportion of Participants Who Progress to Develop Severe and/or Critical Respiratory COVID-19 (ITT) (Day 29)[g]				
Progression Status, n (%)				
No Severe/Critical Progression[c]	412 (93%)	424 (97%)	83 (94%)	90 (100%)
Severe/Critical Progression[d]	25 (6%)	7 (2%)	3 (3%)	0
Category 2: Low flow nasal cannulae/face mask (severe)	11 (2%)	7 (2%)	1 (1%)	0

	No Presence of Moderate to Severe Asthma		Presence of Moderate to Severe Asthma	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	9 (2%)	0	1 (1%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	4 (<1%)	0	0	0
Death	1 (<1%)	0	1 (1%)	0
Missing[e]	4 (<1%)	7 (2%)	2 (2%)	0
Summary of Change from Baseline in Viral Load (log 10 copies/mL) in Nasal Secretions by qRT-PCR at Day 8 (Virology)				
n [f]	266	248	39	46
LS mean change from baseline (standard error)	-2.320 (0.0641)	-2.579 (0.0660)	-2.610 (0.1684)	-2.642 (0.1534)
95% CI	-2.446, -2.194	-2.709, -2.449	-2.941, -2.280	-2.943, -2.340
Difference (standard error)	-0.259 (0.0920)		-0.031 (0.2275)	
95% CI	-0.440, -0.079		-0.478, 0.416	

Day 29 analysis DCO: 27 April 2021.
Source: m.5.3.5.3, SDAP outputs for efficacy, Table 12.41, Table 12.42 Table 12.43 and Table 12.44

a. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
b. Three participants were hospitalised for >24 hours and met the primary endpoint and 1 participant was hospitalised for <24 hours for hyperglycaemia
c. All participants status at admission is Category 1: Room air.
d. Categories were informed by a combination of FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the NIAID ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy.
e. Progression Status "Missing" counts participants with a missing status in the database (if any). Includes 1 placebo participant who withdrew consent prior to treatment and 4 sotrovimab participants (3 withdrew consent prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).
f. Number of participants with analysable data at Day 8.
g. Analysis was not performed as the model did not converge.

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

Number of risk factors

Finally, subgroup results were presented according to number of risk factors with groups defined per the table below. There rate of clinical progressions increased with number of risk factors in both arms. There was no difference in the proportion of primary endpoint progressions in the sotrovimab arm compared with placebo in the 3 or more risk factors subgroup. Five of 6 sotrovimab patients who progressed had at least 3 risk factors, of which 3 were hospitalised for events potentially unrelated to COVID-19.

Table 31: Summary of Primary and Key Secondary Efficacy Endpoints by Number of Risk Factors (≤1, 2, ≥3)

Number of Risk Factors	≤1		2		≥3	
	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)	Placebo	Sotrovimab (500 mg IV)
Number of Participants	307	293	153	178	69	57
Proportion of Participants Who Have Progression of COVID-19 (Hospitalisation >24 hours or Death) (ITT) (Day 29)[a]						
Progression Status, n (%)						
..Hospitalised >24 hours or Death, due to any cause	15 (5%)	0	9 (6%)	1 (<1%)	6 (9%)	5 (9%)
Hospitalised >24 hours for acute management of any illness	15 (5%)	0	8 (5%)	1 (<1%)	6 (9%)	5 (9%)
Death due to any cause	0	0	1 (<1%)	0	1 (1%)	0
..Alive and not hospitalised >24 hours	291 (95%)	288 (98%)	141 (92%)	175 (98%)	62 (90%)	52 (91%)
..Missing[a]	1 (<1%)	5 (2%)	3 (2%)	2 (1%)	1 (1%)	0

Subgroup analysis on serostatus at baseline

Only analysis of anti-nucleocapsid serostatus was conducted.

Table 32: 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.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of efficacy for trial COMET-ICE

Title: A Phase II/III randomized, multi-centre, double-blind, placebo-controlled study to assess the safety and efficacy of monoclonal antibody sotrovimab for the early treatment of coronavirus disease 2019 (COVID-19) in non-hospitalized patients.		
Study identifier	VIR-7831-5001 (COMET-ICE, GSK Study 214367); EudraCT: 2020-002871-36	
Design	Randomised, double-blind, multi-centre, placebo-controlled trial	
	Duration:	24 weeks
Hypothesis	The primary objective of this study was to evaluate the efficacy of sotrovimab (VIR-7831) versus placebo in preventing the progression of COVID-19 disease. The primary endpoint was the proportion of participants with progression of COVID-19 as defined by hospitalisation >24 hours or death through Day 29 and was summarised using counts and proportions of the number of participants who have progression of COVID-19 (defined as hospitalisation >24 hours or death) and was analysed using an exact Poisson regression model with robust sandwich estimators adjusting for duration of symptoms (≤3 days vs. ≥4 days), age (≤70 vs. >70 years old) and gender (male, female). Missing data were imputed under a missing at random (MAR) assumption using a multiple imputation (MI) model. The study used a group-sequential design with 2 planned interim analyses to assess futility due to lack of efficacy and overwhelming efficacy as well as safety. A Lan-DeMets [**Error! Reference source not found.**, 1983] alpha-spending function was used to control the type I error for the primary endpoint, using a Pocock analogue rule for futility and a Hwang-Shih-DeCani (γ = 1)	

	analogue rule for efficacy [Hwang, 1990]. The stopping boundary due to profound efficacy for the first interim analysis (IA1) with N=583 was P<0.02758, which the study met. The study was therefore stopped for enrolment, and all randomised participants continue to be followed until their Week 24 visit (end of study) or early withdrawal. The planned Day 29 analysis to include the primary endpoint and key secondary endpoints was conducted on all randomised participants (N=1057). Secondary endpoints were formally analysed only at the Day 29 analysis and were tested with alpha level of 5% (two-sided). The second interim analysis was not performed.		
Treatments groups	Sotrovimab 500 mg IV		A single intravenous (IV) infusion of sotrovimab 500 mg.
	Placebo		A single IV infusion of equivalent volume of sterile saline solution.
Endpoints and definitions	Primary endpoint	Hospitalised >24 hours or death, due to any cause	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	Emergency room (ER) visit, hospitalised, or death, due to any cause[f]	Proportion of participants who have progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR • Hospitalization for acute management of illness OR • Death
	Secondary	Severe/Critical COVID-19 [f]	Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifested by requirement for and method of supplemental oxygen at Day 29
	Secondary	All-cause mortality	29-day all-cause mortality
Data cut-off (DCO)	Planned IA1 analysis: 04 March 2021 Planned Day 29 Analysis: 27 April 2021		
Results and Analysis			
Analysis description			
Analysis population and time point description	**Analysis of the Primary Endpoint:** ITT (IA1): Data from all participants who were randomly assigned to study intervention by 19 January 2021 and therefore had an opportunity to be followed to Day 29 (N=583). **Day 29 Analysis of Primary Endpoint and Secondary Endpoints:** ITT (Day 29): Data from all randomized participants (N=1057).		
Descriptive statistics and estimate variability		**Placebo**	**Sotrovimab (500 mg IV)**
	Primary Endpoint		

	ITT (IA1)		
	Number of participants	292	291
	Hospitalised >24 hours or death due to any cause	21 (7%)	3 (1%)
	Missing progression status[a]	1 (<1%)	4 (1%)
	Adjusted relative risk ratio (97.24% CI)	0.15 (0.04, 0.56)	
	95% CI	0.04, 0.48	
	p-value	0.002	
	Risk difference	-8.05	
	Adjusted number needed to treat [b]	13	
	ITT (Day 29)		
	Number of subjects	529	528
	Hospitalised >24 hours or death due to any cause	30 (6%)	6 (1 %)
	Missing progression status[c]	5 (<1%)	7 (1%)
	Adjusted relative risk ratio (97.24% CI)	0.21 (0.08, 0.56)	
	95% CI	0.09, 0.50	
	Nominal p-value	<0.001	
	Risk difference	-6.34	
	Adjusted number needed to treat [b]	16	
	Primary Endpoint by Stratification Subgroups		
	Hospitalized >24 hours or death due to any cause [f]		
	≤70 years old	23 (5%)	4 (<1%)
	>70 years old	7 (13%)	2 (4%)
	≤3 days symptom duration	17 (5%)	3 (<1%)
	≥4 days symptom duration [d]	13 (6%)	3 (1%)
	Key Secondary Endpoints (ITT [Day 29])		
	ER visit, hospitalized or death due to any cause [f]	39 (7%)	13 (2%)
	Relative Risk Ratio	0.34	
	95% CI	0.19, 0.63	
	p-value	<0.001	
	Severe and/or critical COVID-19 (D29) [f]	28 (5%)	7 (1%)
	Relative Risk Ratio	0.26	
	95% CI	0.12, 0.59	
	p-value	0.002	
	All-cause mortality (Day 29)	2 (<1%) [e]	0
Notes	Poisson model with robust sandwich estimators; adjusted for age (≤70,>70), duration of symptoms (≤3, ≥4) and gender. Multiple imputation for missing data. Significance level for the IA1 Day 29 α=2.758%. a: 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).		

	b: Number of participants needed to treat in order to prevent 1 additional hospitalisation >24 hour or death by Day 29. 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: As 24 hours was allowed between randomisation and dosing, participants may have been dosed up to 6 days after the onset of symptoms. e: One participant died due to COVID-19 pneumonia and 1 participant died due to pneumonia. f: As per protocol.

2.5.5.3. Clinical studies in special populations

Of the total study population of 1057 subjects, 213 subjects (20%) were 65 years and above. Please refer to the subgroup analysis with regards to efficacy stratified by age.

Table 34: Elderly participants recruited

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	147/1057	53/1057	13/1057

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy programme comprises one pivotal trial. Currently, two phase 2 trials and two phase 3 trials are ongoing, however efficacy data from those trials are not available yet. The trials are examining other drug substances, other administrations, other populations or combination treatment, hence the efficacy data from those studies is not considered relevant for the current efficacy evaluation.

The COMET-ICE study was the subject of three rapid CHMP scientific advice procedures. In principle, the randomised and double-blind design was appropriate. The applicant chose to target patients not hospitalised or requiring supplemental oxygen at baseline, which equates with a population that would be considered to have mild disease (based on the WHO classification schema) and not, as claimed by the applicant, mild to moderate COVID-19. Nevertheless, the proposed indication for use correctly avoids any reference to mild or moderate disease and instead refers to patients not requiring supplemental oxygen, which is appropriate.

As only one single pivotal trial has been conducted, the results should be statistically compelling and clinically relevant.

The pivotal trial, COMET-ICE, is a phase II/III, randomised, multi-centre, double-blind, placebo-controlled study to assess the safety and efficacy of sotrovimab for the early treatment of COVID-19 in non-hospitalised patients. The treatment evaluated was a single 500 mg intravenous infusion of sotrovimab, and the dose was determined based on preclinical studies.

After 583 subjects had completed 29-days follow-up, a pre-planned first interim analysis was conducted. Based on a conclusion from an independent data monitoring committee, the trial was stopped due to efficacy and so was the inclusion of more subjects. The data provided for the current assessment is therefore based on 1057 subjects, which is the number of subjects that were included when the trial was stopped. The subjects included in the current application have been followed for at least 29 days, as this is the duration of follow-up for the primary endpoint.

The planned 24-weeks follow-up has not been completed yet. Those data should be provided in an amendment, when the 24-weeks follow-up has been completed. This amendment should also include the final results on the analysis on variants, immunogenicity and PK, and the results on the secondary endpoint, all-cause mortality at day 60 and day 90 (**REC**).

The study comprised 2 phases: a first in human study and extension part (phase 2/3 study). The lead in phase included 21 subjects randomised 1:1 to sotrovimab or placebo and was included in the main analysis. Although the study setup during the lead-in phase and the main phase differ including unblinding of participants through day 15 due to safety evaluation, the approach is acceptable, as the low number of subjects in the lead-in phase is not considered to have affected the final results.

The inclusion criteria comprised patients ≥ 18 years, symptoms ≤ 5 days, valid positive COVID-19 test, non-hospitalised patients, oxygen saturation ≥ 94%, and several risk factors for COVID-19. The indication includes patients down to 12 years of age, and even though no subjects have been included below the age of 17 years, extrapolation of the results to children down to the age of 12 years is considered acceptable in line with comparable products. There is currently no consensus on risk factors for progression to severe COVID-19, however, the risk factors included in the inclusion criteria in the current study are, besides for asthma, considered relevant risk factors for severe COVID-19.

Presence of SARS-CoV-2 was based on a local result for RT-PCR in 85% and on antigen detection in 15%, such that all patients had a positive result as required in the protocol for eligibility. It is a pity that not all had RT-PCR confirmation in the central laboratory and that central laboratory confirmation was not requisite for inclusion in the primary analysis. Nevertheless, in the midst of a pandemic, even the antigen detection test results were likely accurate in all or most cases.

The exclusion criteria are also considered relevant. No subjects vaccinated with a COVID-19 vaccine were included in the study, which is adequately reflected in the SmPC section 5.1.

The primary objective, "to evaluate the efficacy of sotrovimab versus placebo in preventing the progression of mild/moderate COVID-19" is considered appropriate and supports the claimed indication.

The primary endpoint is defined as the proportion of subjects who were hospitalised more than 24 hours or died during 29 days after sotrovimab treatment as a measure of progression of COVID-19. As hospitalisation and death can be due to other factors than COVID-19, it is not fully agreed with the Applicant that the endpoint is solely a measure of progression of COVID-19, and the primary endpoint is not considered completely supporting the primary objective.

The CHMP did not agree with the change in primary endpoint proposed in the last of the scientific advice procedures. The initial primary endpoint was based on progression to requirement for some level of oxygen supplementation or death. This was defined as development of oxygen saturation <94% on room air on two occasions at least 8 hours apart or hospitalisation requiring some form of oxygen supplementation or death within the 28-day follow-up period. This primary endpoint was deemed appropriate and was agreed. The revised primary endpoint that required only hospitalisation >24 hours or death was considered suboptimal. This was not only because of different thresholds for hospital admission and discharge in different healthcare systems but also because some patients are

hospitalised simply because they cannot be cared for at home for some reason or as a precaution because of other conditions.

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

One of the secondary endpoints is requirement for and method of supplemental oxygen at Day 8, Day 15, Day 22, or Day 29, which is considered a more relevant measure of progression of COVID-19, although this is also dependent on a subjective evaluation and on the availability of supplemental oxygen at the hospitals during a pandemic.

The blinding, randomisation and statistical methods are considered adequate. The randomisation was stratified by region, which is deemed relevant e.g. due to the pandemic. The randomisation was further stratified by age and duration of symptoms, which has also covariates in the analysis. Due to low number of subjects in South America and Europe, the analyses were not adjusted for region.

The primary analysis was based on intention to treat population and Poisson regression analyses was used. Sensitivity analyses and relevant subgroup analyses were conducted. The secondary endpoints were analysed based on a pre-defined hierarchy with a two-sided alpha level of 0.05. Multiplicity was adequately accounted for in the analyses including the interim analysis. Missing values were addressed appropriately.

The plans for the interim analyses that led to the DSMB recommendation to cease enrolment were broadly acceptable. It was very important that analyses for futility were planned due to lack of any data that could predict efficacy.

Efficacy data and additional analyses

A total of 1351 subjects were screened, and of those, 1057 subjects were included in the study and randomised 1:1 to sotrovimab or placebo. In the sotrovimab arm, 10 out of 528 subjects withdraw consent, and in the placebo arm 12 out of 529 subjects withdraw consent. The reasons for withdrawal were similar between treatment arms.

During the study, one protocol amendment was implemented. The amendment included several important changes including objectives, endpoints, inclusion and exclusion criteria, interim analysis and safety measures. As the study was blinded and as the changes were implemented before the database lock, the changes in objectives, endpoints, and statistical analysis plan is not considered to be data driven, and the changes to the protocol are not considered affecting the conclusion of the study. The assumed progression rate in the placebo group was lower than anticipated. For the sample size calculation, the expected progression of COVID-19 rates were 16% in the placebo arm and 10% in the sotrovimab arm. The observed progression rates were much lower: 6% and 1%. The sample size calculation was based on progression rates from data early in the pandemic from Wuhan, China, and New York, which partly explains the differences in the expected and observed progression rates.

Several protocol deviations were present. Overall, the protocol deviations were equally distributed between sotrovimab and placebo. At randomisation 299 subjects (28%) were mis-stratified. This is mainly attributed to miscalculation of the duration of symptoms, relative to the date of screening. This is considered a misunderstanding between the sponsor and the study staff, but it is not an issue of particular concern regarding study conduct. The mis-stratification is similar in both groups, and in the analysis the stratification factor was based on the eCRF and not the assignment at randomisation. This is considered acceptable and is overall not considered to affecting the results. For two of the

participants, an unblinded staff member administered the drug. Even though this is considered a major protocol deviation, it is not expected that those two instances would have affected the main conclusion of the study.

The baseline characteristics were equally distributed across treatment arms. Specifically, the symptoms of COVID-19 and the duration of symptoms and comorbidities were equally distributed. The majority (>70%) had cough, headache, and myalgia, and 59% had symptoms for a duration of 3 days or shorter. More than 50% of the study population were obese, and 20% was above 65 years of age. 22% had diabetes requiring medication, 17% had asthma, 6% COPD, 1% chronic kidney disease and <1% heart failure. Even though not all of the risk factors defined by the Applicant are considered established risk factors for severe COVID-19, and other risk factors for severe COVID-19 exist or might emerge as the evidence evolves, the study population overall reflects the population which could be considered suitable for treatment with sotrovimab and is reflected in the indication.

Concomitant medication for the treatment of COVID-19 was allowed during the study, and convalescent plasma, remdesivir and steroids were used in some of the included subjects. Convalescent plasma was used after hospitalisation for 24 hours and did therefore not affect the primary endpoint. As remdesivir is indicated in patients with need of oxygen supplementation, it is assumed that patients treated with remdesivir stayed at hospital for more than 24 hours and that remdesivir therefore did not impact the primary endpoint. With regards to steroids, information on intensification of treatment was not recorded by the Applicant. However, during the 28 days follow-up, the initiation of steroids was more frequent in the placebo group than in the sotrovimab group. The higher proportion in the placebo group could reflect a worse outcome in this group than in the sotrovimab group, e.g. 13 out of 529 subjects in the placebo group vs 2 out of 528 subjects in the sotrovimab group were treated with iv steroids from day 1 to day 29. Even though the important information on intensification of steroids were not reported during the study, the initiation of steroids was markedly higher in the placebo group compared with the sotrovimab group. As the proportion of subjects treated with steroids was balanced at baseline, the results of the study are not considered biased in favour of sotrovimab.

The intention to treat population comprised 1057 individuals. Missing information on the primary endpoint was relatively low with 5 subjects in the placebo group and 7 subjects in the sotrovimab group. In the placebo group 30 out of 529 subjects and in the sotrovimab group 6 out of 528 subjects 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%, hence the primary endpoint was met. No subjects in the sotrovimab group died, whereas 2 subjects in the placebo group died. According to the Applicant, one subject due to COVID-19 pneumonia and one subject died due to pneumonia. Even though the relative effect was large, the risk difference was around 6%, which is smaller than the estimated effect size for the sample size calculation, as the primary endpoint was not as frequent as expected.

In the sensitivity analysis, where missing values were counted as failures in both treatment arms, the relative risk ratio was 0.38 (95% CI: 0.20;0.70) and the relative risk reduction was 62%. Using a more conservative approach, where missing progression status in the sotrovimab arm was classified as treatment failure (progression) and in the placebo arm as treatment success (no progression), the relative risk ratio case was 0.44 (95% CI: 0.23;0.83, p-value 0.012). Hence, using the most conservative approach for the missing data, there was a statistically significant relative risk ratio of 0.44 corresponding to a relative risk reduction of 56%.

The secondary endpoints supported the primary endpoint and showed statistically significant difference between treatment arms, which is endorsed.

Most importantly, sotrovimab resulted in numerical reductions in need for supplementary oxygen delivered by any means and progression to severe and/or critical respiratory COVID-19.

In fact, no patient treated with sotrovimab required high flow oxygen, oxygen via a non-rebreather mask or mechanical ventilation through Day 29 compared to 14 in the placebo group. These results support a conclusion that sotrovimab influences the risk of disease progression, even though this was not the final primary endpoint of the study.

The secondary endpoints, change in viral load and change in FLU-PRO Plus, are incomplete, no firm conclusion based on those results can be drawn and results should therefore not be reflected in the SmPC. However, as the primary endpoint is met and is supported by statistically and clinically relevant differences in the respiratory secondary endpoint, the data on viral load and FLU-PRO Plus are not expected to have a major impact on the conclusion. The relevant endpoints also including progression of severe and/or critical respiratory COVID-19 are reflected in the SmPC.

The predefined subgroup analyses did not reveal any marked heterogeneity between subgroups of age and duration of symptoms. However, the number of events is low, and the results should be viewed with caution.
The Applicant has provided additional subgroup analyses based on the predefined risk factors (age < / ≥55 years, obesity, diabetes requiring medication, moderate to severe asthma). For obesity, the results were unexpected. The relative risk reduction was largest in the non-obese subjects with a relative risk ratio of 0.06 (95% CI: 0.01;0.42) in non-obese subjects and 0.45 (95% CI: 0.16;1.26) in obese subjects corresponding to a relative risk reduction of 94% and 55%, respectively. Furthermore, the proportion of subjects with a primary endpoint event in the placebo group was larger in non-obese subjects (10%) than in obese subjects (4%) questioning obesity as a risk factor for severe COVID-19. The Applicant has conducted explorative analyses in order to explain this finding, and those analyses showed that the population of obese subjects were on average 10 years younger than the non-obese subjects. As age is a strong risk factor for severe progression of COVID-19, the different age distribution is a plausible explanation for this finding.

Recent evidence suggests that lower levels of early anti-SARS-COV-2 antibody responses to S protein antigens correlate with poor clinical outcomes, and in seronegative hospitalized COVID-19 patients neutralizing antibody treatment yields a beneficial effect, which is not found in subjects who already mounted immune response. Baseline serostatus was based solely on anti-nucleocapsid antibody. It would have been possible to apply several tests including detection of anti-spike antibody. Nevertheless, even based solely on anti-nucleocapsid, the benefit of sotrovimab was driven by the effect of treatment in the subset without anti-nucleocapsid at baseline.

For the risk factor, moderate to severe asthma, the risk of the primary endpoint in the placebo group was lower in subjects with asthma (3%) compared with subjects without asthma (6%), which also questions whether asthma is a risk factor for severe COVID-19. Overall, the subgroup analysis based on the predefined risk factors underlines the challenges in identifying the population at high risk for severe COVID-19.

Very few patients had factors other than being aged at least 55 years, obese and/or diabetic. Due to lack of data, the treatment effect in patients with types of immunodeficiency leading to poor ability to respond to viral infections is unknown. Moreover, while much caution is required when looking at treatment effect by risk factor(s), the sotrovimab patients who did progress as per the primary endpoint were all aged >55, with 2 aged >70 years. Five of the six were obese and all six had diabetes requiring medications. Moreover, there was no difference between sotrovimab and placebo in rates for the primary endpoint among the patients (n= 57 sotrovimab and 69 placebo) with 3 or more of the protocol-defined risk factors.

All persons who become infected with SARS-CoV-2 are "at risk" for progressing to severe COVID-19 even though the risk may be smaller in e.g. a healthy young adult compared to an elderly with comorbidities. With the inclusion criteria for COMET-ICE, it is agreed that the studied population overall is at some level of increased risk for progression to severe COVID-19, also reflected by the hospitalisation rate in the placebo group (7%). The understanding of the most important risk factors is still clearly evolving, and acknowleding the caveat that not all patient populations at increased risk for progression to severe disease were included in the study – the majority were obese and middle-aged, it is still considered appropriate to restrict the indication to a population at increased risk: *Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see section 5.1).*

The updated virology data from COMET-ICE provide limited information on the ability of sotrovimab to treat well-described circulating variants due to the low numbers enrolled with any variant of interest or concern. The data are also limited in terms of assessing the potential effect of sotrovimab epitope variants at baseline or emerging post-treatment on clinical progression. Indeed, the available clinical data, with only three sotrovimab patients admitted to hospital within 29 days due to COVID-19, no conclusions can be drawn on the relationship between mutations and clinical response.

2.5.7. Conclusions on clinical efficacy

The efficacy is based on a single pivotal trial that was stopped early due to efficacy determined based on a predefined interim analysis by an independent data monitoring committee.

The benefit shown in terms of hospitalisation and mortality rates through day 29 is supported by the very important secondary endpoints that captured need for oxygen supplementation and progression to severe disease. The inclusion and exclusion criteria are relevant, and the population included in the study is considered to reflect a population at increased risk for severe COVID-19. As the planned 24-weeks follow-up has not been completed yet, data should be provided in an amendment, when the 24-weeks follow-up has been completed. This amendment should also include the final results on the analysis on variants, immunogenicity and PK, and the results on the secondary endpoint, all-cause mortality at day 60 and day 90 (REC).

2.5.8. Clinical safety

2.5.8.1. 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). Currently, 3 other studies are ongoing, but due 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 the additional supportive studies. 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 the three other supportive studies, these studies are commented below in section Safety data from other studies.

Summary of studies used to characterise sotrovimab safety profile:

Table 35: Summary of Studies used to Characterise Sotrovimab Safety Profile at 500 mg (IV)

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 COMET-ICE study post-dose are shown in **Table 36**

Table 36: 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.

2.5.8.2. Adverse events

Overview of Adverse Events are shown in Table 38. 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. Hereof only 9 (2%) and 8 (2%) were considered drug related (see **Table 38**)

Table 37: 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 38: 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
Source: Table 3.6

Summary of common Adverse Events are displayed in Table 40. 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 also Laboratory findings section.

Table 39: 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
Source: m5.3.5.1, COMET-ICE CSR, Table 3.13

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 participants (1%) in each arm) (see **Table 40**). 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 42). 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 sotrovimab.

Table 40: 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 41: 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
Source: m5.3.5.1, COMET-ICE CSR, Table 3.61

Of the 9 reported hypersensitivity related events, 8 took place beyond 24 hours following administration of sotrovimab.

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).

2.5.8.3. 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. See **Table 42** for Listing of deaths.

Table 42: 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: m5.3.5.1, COMET-ICE CSR, Listing 3 and Listing 12
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. For an overview of Serious Adverse Events see **Table 43**.

Table 43: 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

Source: m5.3.5.1, COMET-ICE CSR, Table 3.18 and Table 3.19

Below is Listing of Serious Adverse Events in the sotrovimab arm. 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 44: Listing of SAEs (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.

The most frequently reported SAEs included (sotrovimab vs. placebo, respectively) were:

- COVID-19 pneumonia (3 [<1%] vs. 20 [4%])
- Pneumonia (0 [0%] vs. 3 [<1%])
- Diverticulitis (2 [<1%] vs. 0 [0%])
- COVID-19 (0 [0%] vs. 2[<1%])
- Acute kidney injury (0 [0%] vs. 2 [<1%])

2.5.8.4. Laboratory findings

A summary of chemistry changes from baseline is provided in the table below. 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 45: 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 below. 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 46: 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.

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

Overview of respiratory status are viewed in Figure 14. Of the participants that needed oxygen supply, participants in the sotrovimab arm only required low flow nasal cannula/face mask whereas participants in the placebo arm more frequently required oxygen and in addition more often needed high oxygen supply (high flow, non-invasive ventilation (NIV) or mechanical ventilation), which was not needed in any of the participant in the sotrovimab arm.

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: COMET-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.

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.

2.5.8.5. 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. In Table 21 is number of adverse events in each age-group shown.

Table 47: Number of AE 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%)

Source: m5.3.5.3, supportive data for safety, COMET-ICE Table 13.12.

An overview of the adverse events stratified by age group showed no clear pattern of age-related adverse events. Of note, diarrhoea had the highest frequency in patients below 55 years. The same was true for elevated transaminases.

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. See **Table 48** below for Adverse Events in participants with renal or hepatic impairment.

Table 48: 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%)

2.5.8.6. Immunological events

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

2.5.8.7. 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.

2.5.8.8. Discontinuation due to adverse events

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.

2.5.8.9. Post marketing experience

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

2.5.9. Discussion on clinical safety

In total the safety of sotrovimab was evaluated in 922 participants. Hereof the **main safety data** was provided for 523 participants in the sotrovimab treatment group (500 mg i.v.) of the clinical placebo-

controlled COMET-ICE study. Of the 523 participants in the sotrovimab arm, 520(>99%) participants were followed through >29 days and 360 (69%) have been followed for >85 days. The remaining safety data is provided for 399 participants from three supportive studies, but not included in the main assessment because these studies included different study population (hospitalized patients), different administration methods or combined sotrovimab with another monoclonal antibody. Considering all these data it should be adequate to characterise the pattern of adverse drug events and to assess the safety adequately. Updated safety data should be provided in an amendment, when the 24-weeks follow-up has been completed (**REC**).

The protocol stated that there was collection of solicited symptoms in diaries. Unsolicited AEs were events not collected in diaries. The applicant previously clarified that patient reported outcomes (PROs) in the COMET-ICE study were used to report COVID-19 symptom severity and frequency (Flu-PRO Plus instrument) or the effect of symptoms of COVID-19 on quality of life (SF-12 Hybrid and WPAI Instruments) but were not used to capture AEs.

The AEs described in the CSR were events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) to an investigator or qualified designee and captured in the eCRF. The reporting of AEs could have occurred through a number of mechanisms in which the participant verbalized an untoward medical occurrence to a qualified site staff member. This includes, but is not limited to, participant/investigator interaction during onsite visits and discussion during regularly scheduled phone calls for active COVID-19 monitoring or subsequent COVID-19 monitoring. Local infusion site and systemic events were not solicited events. In case of such an event, there was a follow up eCRF form, which the investigator was instructed to fill to gather medical contextual information and additional details on these events. **Baseline demographic**, including age and comorbidities in the COMET-ICE patient population was well balanced between the placebo and sotrovimab arm. Of the total safety population, 213 subjects were above 65 years of age and this is considered acceptable in order to provide adequate information on the drug safety in the elderly. Type and number of risk factors were also well 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. Overall, the safety pool seems representative of the target population of COVID-19 patients who are at high risk of progressing to severe COVID-19 and who do not require supplemental oxygen. **Concomitant medication** was present in 88 % in the placebo arm and 90 % in the sotrovimab arm. Dexamethasone, ivermectin and remdesivir were slightly more common in the placebo arm than in the sotrovimab arm. However, the differences are small, and the overall spectrum of concomitant medications are well balanced between the two arms.

The reported **AEs** in the sotrovimab group (22%) was similar to the placebo group (23%). Most of these AEs were mild to moderate. Only 8 (2%) in the sotrovimab arm and 9 (2%) in the placebo arm were considered drug related. The most common AE (≥ 1%) consisted of COVID-19 pneumonia, headache, nausea and diarrhoea and accounts for 68/237 (29%), the events occurred at low frequencies. There was a lower proportion of participants with severe (DAIDS) Grade 3 or 4 AEs in the sotrovimab arm than in the placebo arm (3% vs. 7%, respectively). There is a difference in frequency of Adverse Drug Reaction (evaluated by the Applicant) and Drug-Related Adverse Events (evaluated by the investigators). The Applicant has only considered hypersensitivity reactions as drug related, whereas the investigators have considered rash, pruritus, nausea, infusion site pain, pain, abnormal laboratory values including elevated transaminases, dysgeusia, headache, and insomnia as drug related adverse events. Frequencies of drug related headache and insomnia are low (n=1) and could be due to COVID-19 and not the treatment. Therefore, there is insufficient evidence of a causal relationship between sotrovimab and headache and insomnia. Furthermore, diarrhoea was more frequent in the sotrovimab arm (8 patients in the sotrovimab vs 4 patients in the placebo arm). At baseline 31% in the sotrovimab arm and 34% in the placebo arm had diarrhoea. For other monoclonal

antibodies, diarrhoea is stated as very common in the SmPC. However, sotrovimab is targeting an exogenous viral target and numbers are small. Hence diarrhoea is not considered related to treatment. The number of detected immediate **hypersensitivity** reactions was low in the total population. However, more hypersensitivity reactions were observed in the sotrovimab group n=9 compared to placebo n=5 and thus hypersensitivity might be related to the administration of sotrovimab, as stated in the SmPC. All **infusion-related reactions** (IRR) were low or moderate grade (Grade 1 or 2) and clinically manageable with no life-threatening reactions in the COMET-ICE study. Six patients in the sotrovimab arm had infusion related reactions. Only 1 out of the 6 participants with infusion related reactions is a part of the 9 participants with hypersensitivity reactions in the sotrovimab arm. In the ACTIV-3-TICO study (inclusion of patients hospitalized for COVID-19) potentially life-threatening infusion reactions were observed in two participants, who received sotrovimab, hereof one with severe immediate hypersensitivity reaction. As a consequence of the above potential concerns associated with protein-based infusion therapies including infusion related reactions, hypersensitivity and anaphylaxis continues to exist. Infusion-related reactions is therefore listed in in section 4.8 in SmPC. In ACTIV-3-TICO one immediate IRR occurred following administration of sotrovimab in the form of anaphylaxis.

In the COMET-ICE study participants were observed for 2 hours after infusion for immediate infusion related reactions. Clinical monitoring after infusion is stated in the Posology section (Section 4.2) of the SmPC and an observation of one-hour post-infusion is provided. Of the 9 reported hypersensitivity related events, 8 took place beyond 24 hours following administration of sotrovimab. Based on these data non-immediate hypersensitivity reactions cannot be ruled out. However, the low numbers of occurring and the timely delay and thereby uncertainty, causes that currently there is not sufficient evidence to associate sotrovimab with non-immediate hypersensitivity reactions.

From a theoretical view, based on mechanism of action of neutralizing antibodies it is possible that sotrovimab could exacerbate COVID-19 through an **antibody-dependent enhancement**. The applicant addressed the risk of antibody-dependent disease enhancement by assessing symptoms of a broad array of preferred terms that was reviewed within the renal, cardiac, and pulmonary SOCs. Based on this, in the COMET-ICE study, there have been no clinical suspicion of antibody-dependent disease enhancement after treatment with sotrovimab. Furthermore, preclinical in vitro and in vivo models have not shown evidence of sotrovimab causing antibody-dependent enhancement. The Applicant has highlighted that the incidence of potential ADE (pulmonary, cardiac and renal symptoms) was similar in the two arms, and none of the symptoms were consistent with ADE. Overall, no ADE were observed. Therefore, ADE is not considered a safety concern. The Applicant is stating that there is a theoretical risk of ADE in those with sub-neutralising sotrovimab antibody levels and that they will continue to monitor for ADE throughout the clinical development program and through standard pharmacovigilance methods, which is acknowledged, though it has not been specified how this monitoring is planned.

Serious AEs were numerically more common in the placebo arm than in the sotrovimab arm. In total 11 SAEs occurred in the sotrovimab arm none of them were deemed causally related to study treatment. Three participants had COVID-19 pneumonia, two participants had diverticulitis (both known with a history of diverticulitis), two participants had diabetic complications relating to dysregulated diabetes, but numbers were low, and given that the study population included 22 % study participants with diabetes requiring medication, it is not unexpected during an infection. Single reports of SAEs in the sotrovimab arm were non-small cell lung cancer, small intestinal obstruction, myocardial ischaemia and adenocarcinoma pancreas. The patient with cardiac ischaemia was young (40-49 years) but had a medical history with hypertension, hyperlipidaemia, smoking and congestive heart failure.

No **deaths** were reported in the sotrovimab arm of the study. In the placebo arm 4 deaths were reported. As discussed below, in the ACTIV-3-TICO study (inclusion of patients hospitalized for COVID-19) 11 in the sotrovimab group and 8 in the placebo group died.

Development of **anti-drug antibodies** is overall not considered a safety issue in a one dose treatment regimen. Only if ADAs increase clearance considerably and lower exposure or if the patients once in the future should need the therapy again (new infection with COVID-19) it could potentially be an issue. Ten participants confirmed positive for anti-sotrovimab antibodies at Day 29 (Four of the 10 were positive at Baseline). It is noted that 17 participants were ADA positive at baseline, which probably not reflects anti-sotrovimab antibodies. Overall development of anti-drug antibodies is not a safety issue of concern.

Changes in **clinical chemistry** to outside the normal range occurred at a similar frequency between the arms. Overall, 44 participants had an increase in renal laboratory values that were categorised as severe or life threatening. These severe increases were balanced across the arms. Increases in creatinine could be expected due to COVID-19-associated manifestations (diarrhoea, dehydration, etc.). Therefore, due to the balance between the arms, this does not raise safety concerns. Six patients in the sotrovimab arm met the laboratory criteria for hepatocellular injury vs three in the placebo arm. Overall, the data do not suggest a clear association between liver injury and administration of sotrovimab, and it is agreed that COVID-19 may cause a rise in liver parameters. In each treatment arm some participants needed oxygen supply after inclusion in the study. Of note, participants in the sotrovimab arm only required low flow oxygen, whereas participants in the placebo arm more frequently required oxygen and in addition more often needed higher oxygen supply (high flow, NIV or mechanical ventilation).

When AEs were evaluated across **age groups**, the rate of AEs in each age group was reported and were generally similar in those treated with sotrovimab compared to placebo. Except in patients >85 years here 3 out 5 (60%) in the sotrovimab arm had an AE, whereas 0 out of 7 (0%) in the placebo arm. Otherwise the rate of AEs was generally not increasing with age, as could have been expected. The Applicant has provided an overview of the specific adverse events stratified by age group. There was no clear pattern of age-related adverse events. Of note, diarrhoea had the highest frequency in patients below 55 years. The same was true for elevated transaminases. Due to the small sample size of participants >85 years of age, no meaningful clinical conclusion can be drawn for that population.

As no participants less than 18 years old were enrolled in the clinical trials with sotrovimab, no data are available of this special population. No differences are expected in adolescents. There are no clinical data on human fertility, pregnancy or lactation.

COVID-19 is expected to be more severe in patients with chronic kidney disease. The incidence of AEs in participants with kidney disease was similar between both the treatment arms. Few participants included had severe chronic kidney disease n=13. Overall, AEs were more common in participants with moderate or severe renal impairment. Due to the small numbers of participants with an impaired baseline hepatic function, a meaningful comparison based on baseline hepatic function could not be made. It is agreed that no dose adjustment in patients with hepatic or kidney impairment is needed.

Sotrovimab was administered as a single dose. Thus, no treatment interruption besides incomplete infusion due to AEs was possible per definition. In COMET-ICE no participants experienced an AE that permanently stopped the infusion of sotrovimab or placebo.

Due to the increasing SARS-CoV-2 viral variants the risk for treatment failure of sotrovimab cannot be evaluated conclusively and should be monitored closely in future, to prevent treatment failure.

Additional safety data is also provided from two other sotrovimab monotherapy studies and one study where sotrovimab is administered together with bamlanivimab. In total 399 participants in sotrovimab therapy.

The COMET PEAK study provides only SAE data (blinded). 126 participants have been enrolled and 6 SAEs were reported. The 6 SAE occurred in 4 patients, three of them related to worsening of COVID-19. All of them as judge by the investigator not related to study treatment.

In the ACTIV-3-TICO study of treatment with sotrovimab in patients hospitalised for COVID-19 there was no evidence for 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. As discussed above, 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. A high proportion of serious outcomes can be expected in a population hospitalized for COVID-19. Of note these safety issues do not cause safety issues for this application because the included population are different. Hypersensitivity reactions continues to be deemed as an identified risk, as discussed above. The risk of infusion related reactions is stated in 4.4 and 4.8 of the SmPC.

In the BLAZE-4 study 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.

Due to the increasing SARS-CoV-2 viral variants the risk for treatment failure of sotrovimab cannot be evaluated conclusively and will be monitored through standard pharmacovigilance methods in the future, to prevent treatment failure.

2.5.10. Conclusions on clinical safety

In conclusion, based on data available at present, there are no serious concerns about patients' safety, except for hypersensitivity reactions, which are adequately addressed in the product information. Long-term safety data are still pending. The planned 24-weeks follow-up has not been completed yet. All safety data should be provided in an amendment when the 24-weeks follow-up has been completed (REC).

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 49: Summary of safety concerns

Summary of Safety Concerns	
Missing Information	Use in pregnancy Use in children ≥12 to <18 years old

2.6.2. Pharmacovigilance plan

Table 50: Summary of on-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorisation under exceptional circumstances				
NA				
Category 3- Required additional pharmacovigilance activities				
COVID-19 International Drug Pregnancy Registry (COVID-PR) Planned	To evaluate obstetric, neonatal, and infant outcomes among women who required at least one in-hospital or ambulatory medication for mild to severe COVID-19 at any time during pregnancy and received sotrovimab.	Use in pregnancy	Final study report	31/12/2026
COMET-PACE an open-label study to evaluate pharmacokinetics, pharmacodynamics and safety following a single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of disease progression Planned	To evaluate pharmacokinetics, pharmacodynamics and safety in children with mild to moderate COVID-19 with high risk of progression	Use in children ≥12 to <18 years old	Final study report	30/06/2024

2.6.3. Risk minimisation measures

Table 51: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety concern 1 Use in pregnancy	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.6, Fertility, Pregnancy and Lactation and Section 5.3 Preclinical Safety Data Equivalent wording is included in the patient leaflet Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** COVID-19 International Drug Pregnancy Registry (COVID-PR) Final study report – 31/12/2026
Safety concern 2 Use in children ≥12 to <18 years old	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.2, Posology and method of Administration, Section 5.1, Pharmacodynamic properties, and Section 5.2, Pharmacokinetic properties. Equivalent wording is included in the patient leaflet Section 2 **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Planned open-label study (COMET-PACE) to evaluate pharmacokinetics,

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	pharmacodynamics and safety following single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of progression. Final study report – 30/06/2024

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20.08.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.*

2.8.2. Labelling exemptions

On the basis of article 63.3 of Directive 2001/83/EC, the following exemptions from labelling requirements have been granted temporarily:

- the medicinal product will be supplied as a trilingual pack, i.e. outer and immediate labelling will be printed in English, French and German only;
- package leaflets will be provided as a trilingual leaflet, i.e. in English, French and German only, except for the following Member States which still require the printed package leaflet in their national language(s): Belgium, Bulgaria, Croatia, Czech Republic and Greece;
- omission of country-specific blue box information;
- use of one Global Trade Identification Number (GTIN) within the unique identifier;
- alternative access to the package leaflet and country-specific blue box information in the

national languages of the Member States where the medicinal product is marketed will be provided via a QR code included in the outer packaging and the printed package leaflet (see section 2.8.3).

The duration of the above exemptions will be limited to 3 months after the granting of the marketing authorisation, with the possibility to further extend it on the basis of robust justification and updated information. The marketing authorisation holder will ultimately have to comply with the full labelling requirements.

However, for the first 6 weeks after marketing authorisation only, the medicinal product will be supplied as a bilingual pack, i.e. outer and immediate labelling will be printed in French and English only. No printed package leaflet will be included in this bilingual pack; a card displaying a QR code and corresponding platform will be included instead.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

The derogations above should be seen in the context of the flexibilities described in the Labelling flexibilities for COVID-19 therapeutics (EMA/35618/2021, 12 March 2021) which aims at facilitating the preparedness work of COVID-19 therapeutics developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 therapeutics for EU citizens within the existing legal framework.

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling (i.e. outer carton) and the package leaflet for the purpose of providing statutory information has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: SmPC, package leaflet, blue box information and details of national reporting systems to communicate adverse reactions in all EU official languages.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xevudy (sotrovimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

As regards to the legal status, the CHMP endorsed a medical prescription status in the context of the pandemic situation to allow appropriate flexibility for the access and administration of the medicinal product under the appropriate monitoring recommendations provided in the product information.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication within the initial marketing authorisation process is:

Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see section 5.1).

This drug is aimed at non-hospitalised patients with COVID-19 in order to prevent severe COVID-19. The primary endpoint was hospitalisation more than 24 hours or death. One of the secondary endpoints included oxygen supplementation as a reflection of respiratory function and severity of COVID-19.

3.1.2. Available therapies and unmet medical need

Recently, two monoclonal antibodies Ronapreve (casirivimab/imdevimab) and Regkirona (regdanvimab) have been authorised for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. Besides these, two medicinal products are approved for the treatment of patients requiring oxygen supplementation, which is Veklury (remdesivir) and dexamethasone. However, this population is not included in the indication for the current application.

Ronapreve is also approved for prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kilograms.

Four COVID-19 vaccines are approved in the EU. As the efficacy is not 100%, and as new SARS-CoV-2 variants are emerging, COVID-19 cannot be fully prevented. In persons at high risk for severe COVID-19 with break through infections and in persons not vaccinated, there is an unmet medical need that needs to be addressed.

3.1.3. Main clinical studies

The efficacy programme comprises one pivotal trial, the COMET-ICE study. Currently, two phase 2 trials and two phase 3 trials are ongoing, however efficacy data from those trials are not available yet. The pivotal trial, COMET-ICE, is a phase II/III, randomised, multi-centre, double-blind, placebo-controlled study to assess the safety and efficacy of sotrovimab for the early treatment of COVID-19 in non-hospitalised patients. The inclusion criteria comprised patients ≥18 years, symptoms ≤ 5 days, valid positive COVID-19 test, non-hospitalised patients, oxygen saturation ≥94%, and one or more risk factors for COVID-19. The treatment evaluated was a single 500 mg intravenous infusion of sotrovimab, and the dose was determined based on preclinical studies.

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, the trial was stopped due to efficacy and so 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.

3.2. Favourable effects

For the primary endpoint (hospitalisation or death through day 29), 30 out of 529 subjects in the placebo group and 6 out of 528 subjects in the sotrovimab group had an event. The adjusted relative risk ratio was 0.21 (95% CI: 0.09;0.50) and the corresponding relative risk reduction was 79%. No deaths occurred in the sotrovimab group, whereas two deaths occurred in the placebo group.

For the key secondary endpoint (development of severe and/or critical respiratory COVID-19 through day 29) the relative risk ratio was 0.26 (95% CI: 0.12;0.59), and the corresponding relative risk reduction was 74%.

The change in viral load was also statistically significantly different between treatment arms, and LS mean difference was -0.251 (-0.415; -0.087).

Consistency of results were observed across predefined subgroups of age and duration of symptoms.

In agreement with the data generated using pseudotyped virus, the neutralization data for authentic viruses support a conclusion that the antiviral activity of sotrovimab is maintained against the kappa and delta variants.

Impact of baseline serostatus was evaluated. 70% of participants were seronegative at baseline, balanced across treatment arms and 19% were seropositive 11% had unknown status due to missing serology at baseline. For the seropositive patients, 4/97 in the placebo group and 2/105 in the sotrovimab group met the primary endpoint, hence the benefit of sotrovimab was driven by the effect in the seronegative patients.

3.3. Uncertainties and limitations about favourable effects

Only a flat dose of 500 mg has been examined in adults and no dose response studies have been conducted. Furthermore, the dose and efficacy have been extrapolated to adolescents from the adult study. Therefore, whether 500 mg as a single dose is the best dose in adults is of uncertainty, and whether this is also the case for children above 12 years is unknown.

Presence of SARS-CoV-2 was based on a local result for RT-PCR in 85% and on antigen detection in 15%, such that all patients had a positive result as required in the protocol for eligibility. It is a pity that not all had RT-PCR confirmation in the central laboratory and that central laboratory confirmation was not requisite for inclusion in the primary analysis. Nevertheless, in the midst of a pandemic, even the antigen detection test results were likely accurate in all or most cases.

The updated virology data from COMET-ICE provide limited information on the ability of sotrovimab to treat well-described circulating variants due to the low numbers enrolled with any variant of interest or concern. The data are also limited in terms of assessing the potential effect of sotrovimab epitope variants at baseline or emerging post-treatment on clinical progression. Indeed, the available clinical data, with only three sotrovimab patients admitted to hospital within 29 days due to COVID-19, no conclusions can be drawn on the relationship between mutations and clinical response.

3.4. Unfavourable effects

Overall sotrovimab was well tolerated. The reported AEs in the sotrovimab group (22%) was similar to the placebo group (23%). Most of these AEs were mild to moderate. Only 8 (2%) in the sotrovimab arm and 9 (2%) in the placebo arm were considered drug related. Only infusion related reactions and hypersensitivity were deemed related to sotrovimab treatment.

Infusion related reactions and hypersensitivity

More hypersensitivity reactions were observed in the sotrovimab group n=9 compared to placebo n=5. Individual patients have experienced rash, pruritus, dyspnoea and bronchospasm. Six patients in the sotrovimab arm had infusion related reactions. However, all infusion-related reactions were low or moderate grade and clinically manageable with no life-threatening reactions in the COMET-ICE study.

In the ACTIV-3-TICO study (inclusion of patients hospitalised for COVID-19) potentially life-threatening infusion reactions was observed in two participants, who received sotrovimab, hereof one with severe immediate hypersensitivity reaction (anaphylactic reaction). As a consequence of the above potential concerns associated with protein-based infusion therapies including infusion related reactions, hypersensitivity and anaphylaxis continue to exist.

Serious AEs were numerically more common in the placebo arm than in the sotrovimab arm. In total 11 SAEs occurred in the sotrovimab arm none of them were deemed causally related to study treatment.

No deaths were reported in the sotrovimab arm of the study.

3.5. Uncertainties and limitations about unfavourable effects

The data package was prepared when data on the primary endpoint on all participants were available, which is at day 29 after sotrovimab administration. In the protocol, 24-week follow-up for safety, 60- and 90-day follow-up for all-cause mortality are planned, and data on those parameters and analysis have not been submitted yet, as they are not available yet on the total study population due to the short follow-up. Furthermore, data on variants, immunogenicity and PK are currently incomplete. The Applicant should submit those data, when the follow-up is complete and when the analyses have been conducted. Updated safety data should be provided in an amendment, when the 24-weeks follow-up has been completed (REC).

Antibody-dependent enhancement

From a theoretical view, based on mechanism of action of neutralising antibodies it is possible that sotrovimab could exacerbate COVID-19 through an antibody-dependent enhancement. However, there have been no clinical suspicion of antibody-dependent disease enhancement after treatment with sotrovimab, therefore, ADE is not considered a safety concern. The Applicant is stating that there is a theoretical risk of ADE in those with sub-neutralising sotrovimab antibody levels and that they will continue to monitor for ADE throughout the clinical development program and through standard pharmacovigilance methods, which is acknowledged, though it has not been specified how this monitoring is planned.

Anti-drug antibodies

Development of anti-drug antibodies is overall not considered a safety issue in a one dose treatment regimen. However, it could potentially be an issue if ADAs increase clearance considerably and lower exposure or if the patients once in the future should need the therapy again (new infection with COVID-19). Currently, the observed incidence of post-treatment ADAs has been low, with all titer

values near the sensitivity limit of the assay (titers ≤160); available results from approximately 75% of the participants up to Day 29 are provided. Ten participants confirmed positive for anti-sotrovimab antibodies at Day 29 (Four of the 10 were positive at Baseline). It is noted that 17 participants were ADA positive at baseline, which probably not reflects anti-sotrovimab antibodies.

Use in pregnancy

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.

Use in children ≥12 to <18 years old

Sotrovimab IV pharmacokinetics has not been evaluated in paediatric participants (less than 18 years). The proposed extrapolation to adolescents from 12 years of age weighing at least 40 kg is in line with comparable products.

Adverse events by age group

Based on an overview of the specific adverse events stratified by age group, there was no clear pattern of age-related adverse events. Of note, diarrhoea had the highest frequency in patients below 55 years. The same was true for elevated transaminases. Due to the small sample size of participants >85 years of age, no meaningful clinical conclusion can be drawn for that population.

3.6. Effects Table

Table 52. Effects Table for sotrovimab for the indication: For the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (data cut-off: 27th of April).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint, progression of COVID-19	Hospitalisation > 24 hours or death during 29 days	N (%)	6 (1%)	30 (6%)	Relative risk ratio: 0.21 (0.09;0.50) Hospitalisation can be due to other causes than COVID-19	COMET-ICE
Secondary endpoint, progression of COVID-19	Hospitalisation, ER or death during 29 days	N (%)	13 (2%)	39 (7%)	Relative risk ratio 0.34 (0.19;0.63)	COMET-ICE
Secondary endpoint, severe and/or critical respirator COVID-19	Low flow nasal cannulae /face mask, non-re-breather mask or high flow nasal cannulae /non-invasive ventilation, mechanical ventilation/extra-corporeal membrane oxygenation, or death during 29 days	N (%)	7 (1%)	28 (5%)	Relative risk ratio 0.26 (0.12;0.59)	COMET-ICE

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Viral load	Change in viral load at day 8	Log 10 copies/ml (95 % CI)	-2.610 (-2.726;-2.493)	-2.358 (-2.474;-2.243)	Treatment difference: -0.251 (-0.415;-0.087)	COMET-ICE
Unfavourable Effects						
Hypersensitivity		N(%)	9 (2%)	5(<1%)		COMET-ICE
Diarrhoea		N(%)	8 (2%)	4(<1%)		COMET-ICE
Hepatocellular injury ([(ALT/ALT ULN)/(ALP/ALP ULN)]) ≥5 and ALT ≥3xULN)		N(%)	6 (1%)	3 (<1%)		COMET-ICE
Infusion related reaction		N(%)	6 (1%)	6 (1%)		COMET-ICE
Anaphylaxis		N(%)	1 (0,3%)	0 (0%)		ACTIV-3-TICO

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite of the ongoing vaccination against COVID-19 in the EU there is a medical need for therapeutics for the treatment or (prevent progression) amelioration of COVID-19, especially in subjects who for various reasons are in high risk of severe COVID-19.

In the EU the monoclonal antibodies Ronapreve (casirivimab/imdevimab) and Regkirona (regdanvimab) are now authorised for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

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

Overall, the quality data supports a well-controlled manufacturing process and a high quality of sotrovimab. Most outstanding issues have been satisfactory resolved; however, some data is still pending and will be submitted post-authorisation. These especially concern documentation of the method transfer of a potency assay to the EU DP testing site which is ongoing, and additional validation of some purity methods. In light of the on-going COVID-19 pandemic the submission of these data post-authorisation is acceptable and does not, from a quality point of view, preclude marketing authorization.

Proof of concept has been established in non-clinical studies. While most of the nonclinical studies have been conducted at WuXi AppTech located in China and therefore not EU or OECD GLP certified, regular

inspections by both Belgian authorities and FDA support the validity of the data. VIR-7831 retained effectiveness against e.g. the alpha B.1.1.7, beta B.1.351, gamma P.1, CAL.20C, and B.1.617.2 delta-variants, incl. delta with the E484K mutation (see section 2.4.2.1 for additional details), but a few substitutions (E340A, E340K) were found to reduce susceptibility to VIR-7831 with a >100-fold change in EC50 compared to wild type SARS-CoV-2 virus, and in vitro resistance barrier testing identified E340A as a monoclonal antibody resistant mutant. The nonclinical in vitro data using VIR-7381 and in vivo data using VIR-7381-WT and hamster chimeric S309 did not identify a potential for ADE. The toxicity study package is small but considered sufficient, as the product is a human mAb against a non-endogenous target and no cross reactivity was observed in either monkey or human tissue panels.

The reported EC50 of sotrovimab against the omicron (B.1.1.529) pseudotype was 336.4 ng/mL (2021N495027), representing a 2.7-fold reduction in neutralising activity, compared to the Wuhan spike pseudotype. Due to the radical nature of the changes in the omicron spike, it is supported that results from assays employing authentic omicron SARS-CoV-2 would be valuable.

The pivotal study for this review is the COMET-ICE study: a randomised, double-blind, multi-centre, placebo-controlled efficacy/safety study to assess of sotrovimab for the early treatment of COVID-19 in non-hospitalised participants who are at risk of disease progression. Risk factors included older adults (age ≥55 years) or specific comorbidities, including diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate-to-severe asthma.

The analysis of the primary endpoint showed a clinically relevant relative risk reduction of 79% with VIR-7831 compared with placebo for hospitalisation for > 24 hours or death including 1057 subjects. The secondary endpoints supported the primary endpoint and showed statistically significant difference between treatment arms.

No patient treated with sotrovimab required high flow oxygen, oxygen via a non-rebreather mask or mechanical ventilation through Day 29 compared to 14 in the placebo group. These results support a conclusion that sotrovimab influences the risk of disease progression, even though this was not the final primary endpoint of the study.

The virology data from COMET-ICE provide limited information on the ability of sotrovimab to treat well-described circulating variants due to the low numbers enrolled with any variant of interest or concern. The data are also limited in terms of assessing the potential effect of sotrovimab epitope variants at baseline or emerging post-treatment on clinical progression. Indeed, the available clinical data, with only three sotrovimab patients admitted to hospital within 29 days due to COVID-19, no conclusions can be drawn on the relationship between mutations and clinical response.

The safety data evaluation is based in a total of 1049 participants from COMET-ICE and supportive safety information from ongoing studies for 399 participants treated with sotrovimab. Based on the provided safety data, no safety signal, besides hypersensitivity reactions, which is a well-known risk, managed in the SmPC, has been associated with administration sotrovimab and it was overall well-tolerated.

Sotrovimab treatment could be relevant for severely immunocompromised participants, but these were excluded from the study. Subjects previously vaccinated against COVID19 were also excluded. However, there are no reasons to believe that efficacy or safety would be changed in a patient with symptoms of COVID-19 infection in spite of previous vaccination.

A single dose of 500 mg was selected based on in vitro neutralization data, in vitro resistance data, expected human PK extrapolated from a study in cynomolgus monkeys, and the results of the monkey toxicology study. Sotrovimab appears to be well-tolerated and the proposed single dose of 500 mg iv is

considered acceptable. Extrapolation to adolescents from 12 years of age and with a body weight of at least 40 kg should be justified.

Overall, monotherapy with sotrovimab provided a relevant clinical benefit by reducing the risk of hospitalization or death in the target population of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

3.7.2. Balance of benefits and risks

Overall there is a clinical benefit of monotherapy with sotrovimab by reducing the risk of hospitalisation or death in the target population of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

Based on the provided safety data, no safety signal, besides hypersensitivity reactions, which is a well-known risk, managed in the SmPC, has been associated with administration sotrovimab and it was overall well-tolerated.

The demonstrated benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Xevudy is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xevudy is favourable in the following indication:

Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sotrovimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0240/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.