Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sotrovimab

Proprietary Product Name: Xevudy

Sponsor: GlaxoSmithKline Australia Pty Ltd

August 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations 4

I. Introduction to product submission 6

Submission details 6

Product background 7

Regulatory status 9

Product Information 11

II. Registration timeline 11

III. Submission overview and risk/benefit assessment 12

Quality 12

Nonclinical 14

Clinical 15

Risk management plan 44

Risk-benefit analysis 46

Outcome 54

Attachment 1. Product Information 57

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Antidrug antibody
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate transaminase
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}28d}$	Area under the concentration versus time curve from time zero (dosing) to Day 28
$AUC_{0\text{-}7d}$	Area under the concentration versus time curve from time zero (dosing) to Day 7
$AUC_{0\text{-}inf}$	Area under the concentration versus time curve from time zero (dosing) extrapolated to infinity
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
EC_{50}	50% (half maximal) effective concentration
EC_{90}	90% maximal effective concentration
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drugs Administration (United States of America)
GLP	Good Laboratory Practice(s)
GVP	Good Pharmacovigilance Practice(s)

Abbreviation	Meaning
IV	Intravenous
mRNA	Messenger ribonucleic acid
NOAEL	No observed adverse effect level
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
US(A)	United States (of America)
VIR-7831	Drug development code for sotrovimab
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Xevudy
Active ingredient:	Sotrovimab
Decision:	Approved for provisional registration
Date of decision:	20 August 2021
Date of entry onto ARTG:	20 August 2021
ARTG number:	364110
, *Black Triangle Scheme:*[1]	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd Level 3, 436 Johnston Street Abbotsford, VIC, 3067
Dose form:	Concentrated injection solution for infusion
Strength:	500 mg in 8 mL (62.5 mg/mL)
Container:	Vial
Pack size:	Single dose
Approved therapeutic use:	*Xevudy has provisional approval 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 initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalisation or death (see Section 5.1 Pharmacodynamic properties, clinical trials).* *The decision has been made on the basis of short term efficacy and safety data. Continued approval of this indication depends on the*

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.
Route of administration:	Intravenous infusion
Dosage:	*Adults and adolescents (aged 12 years and older and weighing at least 40 kg):* The recommended regimen is a single 500 mg dose administered as an intravenous infusion. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B2 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register Xevudy (sotrovimab) 500 mg in 8 mL concentrated injection solution for infusion for the following proposed indication:

> *For the treatment of patients with coronavirus disease 2019 (COVID-19) who are at risk for progression to hospitalisation or death.*

Coronavirus disease 2019

Coranavirus disease (2019) or COVID-19 is a contagious disease caused by the spread of a virus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The SARS-CoV-2 virus is an enveloped, positive-sense, single stranded ribonucleic acid (RNA) betacoronavirus. SARS-CoV-2 has spread rapidly and globally since its emergence, causing COVID-19. The World Health Organization (WHO) declared that the outbreak

constituted a public health emergency of international concern on 30 January 2020, and declared the outbreak to be a pandemic on 11 March 2020.[2,3]

It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear between 2 to 14 days after exposure to the virus. Symptoms may include fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhoea. Infections caused by the SARS-CoV-2 virus, and the resulting disease, COVID-19, have spread globally.

Since its emergence, the SARS-CoV-2 virus has spread rapidly around the globe. It was officially declared a pandemic by WHO on 11 March 2020. As of 10 August 2021, there have been over 203 million confirmed cases of COVID-19, including over 4.3 million deaths reported to WHO, with the highest number of cases having been reported in the USA, followed by India and Brazil.[4] In Australia, as of 11 August 2021, there have been 37,372 cases and 944 deaths reported.[5] Following suppression of the initial outbreak in early 2020, the situation in Australia has been characterised by periods of zero community transmission, interspersed with sporadic outbreaks caused by escape of the virus from the hotel quarantine system that has been used for returning overseas travellers. At the time this submission underwent final consideration for approval, the relevant public health units are struggling to contain outbreaks in Sydney and south-eastern Queensland caused by the SARS-CoV-2 virus, delta variant of concern. As of 11 August 2021, cases of community transmission in Sydney have occurred at the rate of 344 per day., despite a city-wide lockdown having been in place for over one month.

Current treatment options

Treatment for COVID-19 is mainly supportive, as specific SARS-CoV-2-targeted options are limited. Therapeutics under investigation include antivirals, antibodies and immunomodulators, in addition to several preventative vaccines in various stages of development. At present there are very few products on the Australian Register of Therapeutic Goods (ARTG) with a COVID-19 indication, and none have full registration (they are instead approved under the provisional pathway):

- COVID-19 therapeutics:
  - Veklury (remdesivir), provisionally registered on 10 July 2020 for the treatment of COVID-19 in adults and adolescents (aged 12 years and older, weighing at least 40 kg) with pneumonia, requiring supplemental oxygen.[6]
- COVID-19 vaccines:
  - Comirnaty (BNT162b2; messenger ribonucleic acid- (mRNA) based vaccine); also known as the Pfizer/BioNTech COVID-19 vaccine, provisionally approved

[2] Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). 30 January 2020. Available at: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)
[3] WHO Director-General's opening remarks at the media briefing on COVID-19. 11 March 2020. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
[4] WHO COVID-19 Dashboard (last viewed 11 August 2021, available at: https://covid19.who.int/))
[5] Australian Government Department of Health, as of 11 August 2021. Available at: https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers#how-australia-compares-with-the-world
[6] AusPAR for Veklury remdesivir Gilead Sciences Pty Ltd PM-2020-01491-1-2 available at: https://www.tga.gov.au/auspar/auspar-remdesivir

25 January 2021 for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older;[7]

  - § provisional approval was extended (extension of indications) on 22 July 2021 to include immunisation adolescents aged 12 years and over.[8]

- COVID-19 Vaccine AstraZeneca (ChAdOx1-S), an adenoviral vectored vaccine, provisionally approved 15 February 2021 for active immunisation of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.[9]
- COVID-19 Vaccine Janssen (Ad26.COV2.S), an adenoviral vectored vaccine, provisionally approved on 25 June 2021 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.[10]
- Spikevax (elasomeran); a mRNA-based vaccine, also known as the Moderna vaccine, provisionally approved on 9 August 2021 for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 18 years of age and older.[11]

Vaccine rollout has been affected by supply issues, as well as concerns over the emergence of rare events of thrombosis with thrombocytopenia syndrome in association with the AstraZeneca vaccine.[12] As of 11 August 2021, around 45% of the eligible population aged over 16 years has received a single dose of vaccine, and just under 24% has received both doses.[13] The majority of the Australian population at present remains unvaccinated and vulnerable to the effects of COVID-19.

There remains an urgent need for effective therapeutics and/or preventive vaccines to reduce the burden and spread of disease.

Regulatory status

This product is considered a biological entity for Australian regulatory purposes.

At the time the TGA considered this application, emergency use /temporary authorisations had been approved in the United States of America (USA) on 26 May 2021 (Emergency Use Authorization); Canada on 30 July 2021 (Interim Order); Singapore on 30 June 2021 (Pandemic Special Access) and Italy on 29 July 2021 (Temporary Authorization). Similar applications have also been approved in the United Arab Emirates, Bahrain, Kuwait Qatar and Egypt.

In the European Union (EU) a procedure similar to an application for an emergency use/temporary authorisation was initiated on 14 April 2021. This was a referral procedure under Article 5(3) of Regulation 726/2004. This procedure concluded on

[7] AusPAR for Comirnaty BNT162b2 (mRNA) Pfizer Australia Pty Ltd PM-2020-05461-1-2
available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna-comirnaty
[8] AusPAR for Comirnaty BNT162b2 (mRNA) Pfizer Australia Pty Ltd PM-2021-02187-1-2
available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna
[9] AusPAR for COVID-19 Vaccine AstraZeneca ChAdOx1-S AstraZeneca Pty Ltd PM 2020 06115 1-2
available at: https://www.tga.gov.au/auspar/auspar-chadox1-s
[10] AusPAR for COVID-19 Vaccine Janssen Ad26.COV2.S Janssen-Cilag Pty Ltd PM-2020-06173-1-2
available at: https://www.tga.gov.au/auspar/auspar-ad26cov2s
[11] AusPAR for Spikevax elasomeran Moderna Australia Pty Ltd PM-2021-02994-1-2
available at: https://www.tga.gov.au/auspar/auspar-elasomeran
[12] TGA alert on the use of AstraZeneca ChAdOx1-s COVID vaccine;
available at: https://www.tga.gov.au/alert/astrazeneca-chadox1-s-covid-19-vaccine-3
[13] Australian Government Department of Health: Australia's COVID-19 vaccine rollout.
Available at: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/australias-covid-19-vaccine-rollout

20 May 2021 with a positive scientific opinion being issued by the Committee for Medicinal Products for Human Use (CHMP) and a Conditions of Use document being issued.

At the time that this application for a provisional marketing authorisation was submitted as a 'rolling review' in Australia similar applications were made in parallel to both the European Medicines Agency (EMA) and Switzerland.

Table 1: International regulatory status shown below, gives details of the status and approved indications for approved or ongoing submissions across different regions.

Table 1: International regulatory status

Region/Country	Status	Approved indications
European Union (Marketing Authorisation Application)	Under consideration (rolling submissions). Guidance on the emergency use of sotrovimab was granted on 21 May 2021.	Under review
United States of America (Emergency Use Authorization)	Approved 26 May 2021	*Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [see Clinical Trial Results and Supporting Data for EUA (18)].*
Canada (Interim Order)	Approved 30 July 2021	*Treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) who are at risk for progression to hospitalization or death*
Singapore (Pandemic Special Access Route)	Approved 30 June 2021	*The treatment of adult patients 18 years of age and above with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. The risk factors include greater than or equal to 55 years, diabetes, obesity (BMI* [body mass index] *> 30 kg/m^2), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and/or moderate to severe asthma*
Switzerland (Temporary Authorisation)	Under consideration	Under consideration

Region/Country	Status	Approved indications
Switzerland (Marketing Authorisation Application)	Under consideration	Under consideration
Italy (Temporary Authorization)	Approved 29 July 2021	*Treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Data was provided as a rolling submission. Under normal circumstances, TGA's assessment (for both provisional and general registration) begins once all information to support registration is available. As part of the Department of Health's response to the pandemic, the TGA has agreed to accept rolling data for COVID-19 vaccines, to enable early evaluation of data as it comes to hand.

Table 2: Timeline for Submission PM-2021-01848-1-2

Description	Date
Designation (Provisional)[14]	13 April 2021
Submission dossier accepted and evaluation commenced	20 May 2021
Evaluation completed	13 August 2021

[14] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.

The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.

Description	Date
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	8 August 2021
Sponsor's pre-Advisory Committee response	10 August 2021
Advisory Committee meeting	12 August 2021
Registration decision (Outcome)	20 August 2021
Completion of administrative activities and registration on the ARTG	20 August 2021
Number of working days from submission dossier acceptance to registration decision*	65

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

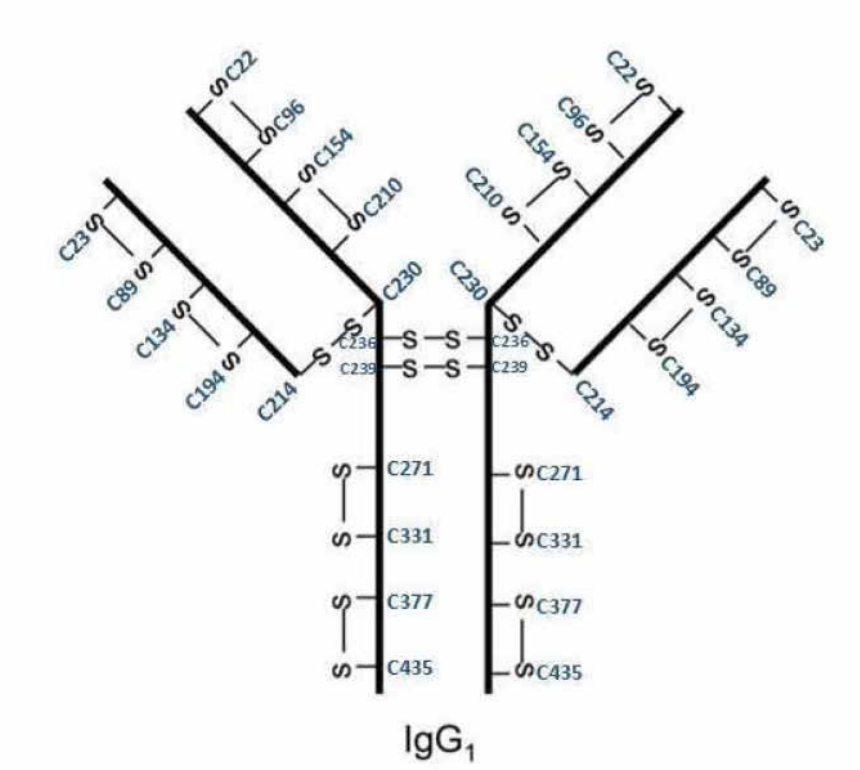
The submission was summarised in the following Delegate's overview and recommendations.

Quality

Sotrovimab is an engineered human immunoglobulin G monoclonal antibody that binds to a highly conserved epitope on the spike (S) protein receptor binding domain of the SARS-CoV-2 virus.

The sotrovimab Fc region has also been engineered to provide an extended half-life through inclusion of LS mutation which enhance FcRn binding. Sotrovimab is produced in Chinese hamster ovary cells and consists of 2 heavy chains and 2 light chains with 2 light chain and 4 heavy chain interchain and 4 intrachain disulfide bonds, as presented in the following Figure 1.

Figure 1: Sotrovimab structure



Sotrovimab immunoglobulin G subtype 1 (IgG1) structure. Disulfide bonds are represented by S-S in the diagram. The 2 dark vertical and diagonal lines represent 2 heavy chains, and with a total of 4 intrachain disulphide bonds each, and 2 interchain disulfide bonds between these heavy chains. The 2 light chains are represented by the diagonal lines, and contrain two intrachain disulphide bonds each. The 2 heavy chains are linked together by two interchain disulfide bonds, and each heavy and light chain is linked together by a single interchain disulphide bond.

Sotrovimab 62.5 mg/mL drug product is a sterile liquid supplied in a single use vial. The drug product is formulated in L-histidine/ L-histidine monohydrochloride buffer; sucrose and polysorbate 80, L-methionine, and water for injection. The vials include a 0.6 mL overfill and are filled to a target fill volume of 8.6 mL to allow for a deliverable volume of 8 mL.

The proposed shelf life for the current products is 12 months and the storage condition is 'Store refrigerated between 2 to 8°C' and 'Store in the original carton in order to protect from light' and 'Do not freeze or shake'. Note that the latter storage directives are not worded in a way that TGA has approved. Also, the submitted data do not indicate that the drug product is particularly susceptible to light and freezing. The quality evaluator will accept it as a precautionary statement. However, this will be evaluated in future when the sponsor applies for Australia specific label. From a quality perspective, the testing parameters and acceptance criteria are acceptable.

Conclusion

From a quality perspective, there were no issues precluding the approval of Xevudy sotrovimab.

Nonclinical

The submitted nonclinical dossier was in accordance with the relevant International Conference on Harmonisation guideline for the nonclinical assessment of biological medicines.[15]

Sotrovimab is derived from an antibody of a B-cell of a SARS-CoV-2 survivor. *In vitro*, sotrovimab bound to recombinant SARS-CoV-2 spike receptor binding domain with high affinity (half-maximal effective concentration (EC_{50}): 20.40 ng/mL, disassociation constant: 0.21 nM). *In vitro* assessment using SAR-CoV-2 virus (pseudovirus and authentic) showed that sotrovimab neutralised effectively the wild-type, beta (B.1.351) and gamma (P.1) variants, and there was a 3 to 4 fold increase in EC_{50} to 90% effective concentration (EC_{90}) for the alpha (B.1.1.7) variant. Sotrovimab neutralised the delta (B1.617 and B.1.617.2) variant pseudovirus, and its activity against the authentic virus was not assessed.

In vivo in the hamster model, sotrovimab decreased antiviral activity infectious virus and virus RNA in lungs and clinical disease (assessed as improved weight loss or lung pathology). In the hamster model a range of doses from sub-neutralising up to fully neutralising antibodies showed no evidence of non-FcγR mechanisms of antibody-dependent enhancement of disease.

While *in vitro* and *in vivo* data lend some support to the proposed use of sotrovimab for the proposed clinical indication, the treatment regimen in the hamster model was preventative. Whilst *in vitro* results with SAR-CoV-2 viruses suggest efficacy against the wild-type, beta and gamma variants and a 3 to 4 fold decrease in activity against the alpha variant, there is insufficient information on the delta variant, although activity against all these variants were demonstrated in in vitro pseudovirus assays.

In vitro resistance studies revealed variants with mutations at E340 and P337 of the receptor binding domain are resistant to sotrovimab. Naturally occurring mutations at these sites are low; however, E340 mutation was the most common in clinical studies.

Amino acid modification in sotrovimab development did not have any effect on effector function.

Studies with remdesivir or bamlanivimab, sotrovimab showed additive antiviral effect with no antagonism with either agent.

No off-target sites were identified in a panel of monkey or human tissues (including a range of human embryofetal proteins).

Sotrovimab did not affect functions of the cardiovascular, respiratory or central nervous systems in monkeys.

Only limited tissues were examined in the distribution study. Highest levels were detected in highly perfused tissues that included lungs, myocardium, liver, kidneys and spleen.

Repeat-dose toxicity studies by the intravenous (IV) route were conducted in cynomolgus monkeys (up to 2 weeks) at exposures > 50 times the clinical exposure based on the area under the concentration versus time curve (AUC). No drug-related toxicities were observed.

No genotoxicity or carcinogenicity studies were submitted. Given the protein nature of the drug and the proposed indication, this is considered acceptable.

No reproductive toxicity studies were submitted. Based on an absence of effects on the reproductive organs in the repeat dose toxicity study, effects on fertility are not predicted. Since the target of sotrovimab is not expressed in humans and there was no cross-

[15] ICH guideline S6 (R1): preclinical safety evaluation of biotechnology-derived pharmaceuticals.

reactivity with human embryofetal proteins, the potential for effects on embryofetal development is expected to be low.

There are no objections on nonclinical grounds to the registration of Xevudy for the proposed indication provided clinical studies provide adequate dose, timing and efficacy data against variants.

Conclusions and recommendation

Pharmacology results suggest efficacy against the wild type, beta and gamma variants and reduced activity against the alpha variant; however, there is insufficient information on the delta variant.

Mutations at E340 and P337 of the receptor binding domain are resistant to sotrovimab. The potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab would need to be monitored clinically.

No toxicity was observed in a study in monkeys at high doses.

There are no nonclinical objections to provisional approval of sotrovimab provided clinical studies provide adequate dose, timing and efficacy data against variants.

Clinical

Clinical data evaluable for the propose indication

The clinical submission is primarily supported by the Day 29 analysis of the COMET-ICE trial (also referred to as Study 214367); the COMET-ICE clinical study report dated 24 June 2021 was submitted.

Also included were:

- a population pharmacokinetics (PopPK) report from the COMET-ICE trial;
- a COMET-ICE trial virology report; and
- literature references

Guidance

Relevant guidance documents for this submission include:

TGA-adopted European Medicines Agency (EMA) guidance relevant to the submission:

- Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2);[16]

Additional guidance (not TGA-adopted):

- US Food and Drugs Administration (FDA): COVID-19: developing drugs and biological products for treatment or prevention: guidance for industry (February 2021).[17]

[16] Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-monoclonal-antibodies-intended-vivo-clinical-use_en.pdf
[17] Available at: https://www.fda.gov/media/137926/download

Pharmacology

Pharmacokinetics

Given the urgency to develop treatments for COVID-19, the well understood pharmacokinetics (PK) and safety profile of human monoclonal antibodies and inability to assess all potential safety risks for COVID-19 participants from healthy volunteers (who lack viral antigen), no healthy volunteer study was conducted.

Human clinical PK data were confined to the single pivotal study in subjects with COVID-19, the COMET-ICE trial (Study 214367). Based on non-compartmental analysis of intensive PK data in the lead-in phase of the COMIT-ICE trial:

- The median time of occurrence of maximum observed concentration (T_{max}) was 0.04 days, consistent with the end of infusion. The mean of maximum observed concentration (C_{max}) was 219 µg/mL.
- The mean steady-state volume of distribution was 8.1 L, indicating limited distribution outside the vascular space, which is consistent with other immunoglobulin G antibodies.
- Sotrovimab has a median elimination half-life of 48.8 days, which is longer than Fc-unmodified immunoglobulin G due to a modification referred to as the LS modification. The mean clearance was 125 mL/day.
- No dedicated studies were conducted to evaluate PK of sotrovimab in special populations, however, population pharmacokinetics (PopPK) was used to inform on dosing recommendations in special populations.

Partial sparse serum PK through study Day 29 from 363 participants in the expansion phase of COMET-ICE trial (Study 214367) was available to date. The mean serum concentration of sotrovimab on study Day 29 was 25.8 µg/mL.

Absorption

No absorption studies have been conducted with sotrovimab. Sotrovimab is administered by IV infusion and the assumed bioavailability is 100 %. When sotrovimab was administered by IV infusion, C_{max} was observed at the end of the infusion with a mean value of 219 µg/mL in the lead-in phase of the COMET-ICE trial.

Distribution

Based on non-compartmental PK analysis from the lead-in phase of the COMET-ICE trial, the mean steady-state volume of distribution of sotrovimab was 8.1 L.

The PopPK model estimated the total volume of distribution for an 87 kg subject to be 11.5 L

Metabolism

Sotrovimab distributes into serum and interstitial space and is degraded by proteolytic enzymes, which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Based on a non-compartmental analysis of intensive PK data, the mean systemic clearance was 125 mL/day. The median terminal-phase elimination half-life was 49 days. The PopPK model estimated that for an 87 kg subject, systemic clearance is 192 mL/day and terminal half-life is 44.3 days.

Population pharmacokinetic data

For the population PK (PopPK) analysis, the dataset consisted of the available PK data from a single study (the COMET-ICE trial, Study 214367). A total of 503 participants

(10 participants included in the lead in phase and 493 included in the expansion phase) received the drug and were included in the sotrovimab population PK analysis data set. Dense PK sampling was implemented for the lead-in phase, with sparse sampling for expansion phase of the study.

Pharmacokinetic data is well described by an IV bolus two compartment model with first-order elimination. There were no model misspecifications of concern based on the diagnostic plots. The observed data is described well by the model and model predictions based on the visual predictive check plots.

Further adjustment to account for the two different populations (lead in versus 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.

A preliminary PopPK, including covariates, was developed using the data available to date from 476 participants.

Apart from body weight and body mass index, other covariates such as age, estimated glomerular filtration rate, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, disease, country, gender, race, ethnicity and anti-sotrovimab antibodies (anti-drug antibodies; ADA) did not influence the PK.

Given the flat dosing, the magnitude of effect of body weight (and body mass index) on the sotrovimab, exposure/PK is considered clinically not meaningful. For reference, over a body weight range of 40 to 160 kg the magnitude of effect of body weight on sotrovimab exposure (serum concentration) is 1.88 to 0.61 times the reference exposure for 87 kg. This range is not considered clinically relevant and dose adjustment by body weight is therefore not recommended. Similarly, over a body mass index range of 25 to 40, the magnitude of effect of body mass index on sotrovimab exposure is (0.9 to 1.10) times the reference exposure for 32 kg/m^2 body mass index. This range is not considered clinically relevant and dose adjustment is therefore not recommended.

Sotrovimab, like other immunoglobulins, is not eliminated intact in urine, thus renal impairment is not expected to affect the exposure of sotrovimab. Based on the clinical pharmacology and some historical data with large molecules, it is unlikely that the renal function will have any influence on the PK of large molecules. As such, no dedicated clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Additionally, renal function was not found to be a significant covariate in the population PK analysis and thus no dose adjustment is expected to be required in participants with renal impairment.

Sotrovimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, thus changes in hepatic function are unlikely to have any effect on the elimination of sotrovimab. No dedicated clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of markers of liver inflammation such as bilirubin and aspartate transaminase (AST) as well as mild to moderate elevations in alanine transaminase (ALT) (1.25 to < 5 x the upper limit of normal; ULN) on the PK of sotrovimab were evaluated by a population PK analysis. Hepatic markers were not significant covariates of sotrovimab exposure. No dose adjustment is expected to be required in participants with hepatic impairment.

No formal drug interaction studies have been conducted. Interactions with concomitant medications that are renally excreted or that are substrates, inducers or inhibitors of

cytochrome P450 (CYP)[18] enzymes are unlikely, since sotrovimab is not renally excreted or metabolised by CYP enzymes.

Due to their high molecular weight, monoclonal antibodies are unlikely to have direct ion channel interactions. Furthermore, Good Laboratory Practices (GLP)[19] tissue cross-reactivity studies in normal human tissues did not identify off-target binding and no toxicity was identified in a GLP cynomolgus monkey 2 week repeat dose IV infusion toxicology study. Therefore, a thorough QT duration corrected for heart rate (QTc)[20] study has not been conducted for sotrovimab.

Immunogenicity

During clinical development, immunogenicity was assessed using a risk-based bioanalytical strategy. Ten subjects out of 503 were ADA positive on Day 29. Anti-sotrovimab antibodies (ADAs) 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. Sotrovimab is proposed to be administered as a single dose, which theoretically reduces the risk of immunogenicity compared with multiple doses. Overall, the observed incidence of post-treatment anti-sotrovimab antibodies has been low. The clinical relevance of such antibodies has not been fully established. Immunogenicity will continue to be assessed in the COMET-ICE trial (Study 214367). Anti-drug antibodies were evaluated as a covariate in the PopPK model and did not influence serum concentrations.

Paediatric patients

The sponsor proposes dosing in adolescents aged 12 years and older and weighing at least 40 kg; however, there are no clinical data available in subjects aged under 18 years. This proposal is based on an allometric scaling approach implemented in the model which accounts for effects of body weight changes associated with age on clearance and volume of distribution, and relies on the conclusion of the PopPK analysis that no dosage adjustment is required across subject weight range 40 to 160 kg.

To this end, the expected peak (C_{max}) and average exposures (as area under the drug-concentration curve versus time curve from time 0 (dosing) to Day 28; $AUC_{0\text{-}28d}$) in 40 kg adolescents are anticipated to be (48 out of 40) or 1.0 and (48 out of 40) or 0.75 times higher than the 48 kg reference, that is, 120% and 115%, respectively and would be expected to afford approximately 46 fold C_{max} and 37 fold the area under the drug-concentration versus time curve from time zero (dosing) extrapolated to infinity ($AUC_{0\text{-}inf}$) cover compared with the preclinical 500 mg/kg no-observed-adverse-effect level

[18] **Cytochrome P450 (CYP) enzymes**: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.
[19] **Good Laboratory Practice** or **GLP** is a quality system of management controls for research laboratories and organisations to ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of products in development for human or animal health (including pharmaceuticals) through non-clinical safety tests; from physio-chemical properties through acute to chronic toxicity tests.
[20] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The **corrected QT interval** (**QTc**) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

(NOAEL). Such small differences in peak and average exposure are within subject-to-subject variation, justifying the lower weight limit for the modest (22%) proportion of adolescents in the range 40 to 48 kg (based on simulation from NHANES data).[21] Since adolescents are, on average, lighter than adults, sotrovimab exposure will be marginally above adults, hence the risk of under-dosing adolescents with the same 500 mg IV dose is small. Furthermore, human exposure cover is anticipated from the bodyweight range of adults treated with sotrovimab in the COMET-ICE trial/Study 214367 (49 to 183.0 kg). The sponsor therefore proposes the same dosing recommendation for adolescents (aged 12 to less than 18 years and weighing 40 kg or more) as adults.

Pharmacodynamics

Properties related to therapeutic effect

Sotrovimab is a Fc modified human immunoglobulin G subtype 1 monoclonal antibody that binds to a highly conserved epitope on the spike (S) protein receptor binding domain of the SARS-CoV-2 virus with high affinity outside of the receptor-binding motif, where the majority of the other COVID-19 monoclonal antibodies in development bind.

Binding to this highly conserved region precludes resistant variant selection *in vitro* and allows sotrovimab to retain activity *in vitro* against SARS-CoV-2 viral mutants. Sotrovimab neutralises SARS-CoV-2 live virus and pseudotyped virus *in vitro* and retains activity against the alpha, beta, gamma live viruses, as well as epsilon, iota and kappa variant pseudotyped viruses. The Fc domain of sotrovimab includes an LS modification that extends antibody half-life and may also be expected to enhance distribution to the respiratory mucosa. The LS modification does not impact wild type Fc-mediated effector functions and sotrovimab demonstrates activity in two key indirect antiviral mechanisms antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis *in vitro*, which may also contribute to clinical effectiveness.

SARS-CoV-2 viral load

The sponsor has not proposed a primary clinical pharmacodynamics biomarker. The effect of sotrovimab on viral load in nasal secretions was a secondary efficacy endpoint of the pivotal study. This showed a statistically significant reduction versus placebo on Day 8 (least squares of the mean difference -0.232, p = 0.007), but the clinical relevance of the magnitude of the difference is not clear.

Genetic, gender and age related differences in pharmacodynamic response

A subgroup analysis of the Day 8 viral load data suggests that the difference observed between sotrovimab and placebo was greatest in those aged 55 years or more, and that there was no significant difference in those aged under 55 years.

[21] The **National Health and Nutrition Examination Survey** (**NHANES**) is a program of studies designed to assess the health and nutritional status of adults and children in the United States of America (USA). The survey is unique in that it combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics (NCHS). NCHS is part of the Centers for Disease Control and Prevention (CDC) and has the responsibility for producing vital and health statistics for the USA. Findings from this survey are be used to determine the prevalence of major diseases and risk factors for diseases. Information is used to assess nutritional status and its association with health promotion and disease prevention. NHANES findings are also the basis for national standards for such measurements as height, weight, and blood pressure. Data from this survey are used in epidemiological studies and health sciences research.

Efficacy

Dose justification

The pivotal study, the COMET-ICE trial (Study 214367), was also the first in human study, so no human *in vivo* data were available to inform dosage selection. The justification for the selected dose was based on *in vitro* data and non-human primate studies.

No dose response study has been conducted. Only one dose of 500 mg has been investigated. The sponsor justifies that 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.

The human PK parameters were scaled from the cynomolgus monkey using an allometric scaling approach for human immunoglobulin G antibodies (allometric coefficient of 0.85 and 1 for clearance and volume of distribution, respectively). This resulted in a predicted serum clearance in 70 kg humans of 141 mL/day, an estimated volume of distribution of 6500 mL (approximately 93 mL/kg) and projected half life of around 32 days.

Following a 500 mg IV dose of sotrovimab, the mean Day 29 serum concentration was 25.8 µg/mL (95% confidence interval (CI): 25.0, 26.7). Based on the available PK, a 500 mg IV dose of sotrovimab is expected to maintain serum levels at or above 25 x lung tissue adjusted EC_{90};[22] for 28 days in 50% of participants and at or above 15 x lung tissue adjusted EC_{90} for 28 days in 95% of participants; this is based on the EC_{90} (0.33 µg/mL) from the highest end of the EC_{90} range and accounting for the lung: serum ratio for immunoglobulin G antibodies (assumed conservative value of 0.25 (lung tissue adjusted EC_{90} = 1.32 µg/mL); measured and reported range 0.25 to 0.68 for whole lung and interstitial fluid, respectively.

Human exposure following a 500 mg single IV dose is considerably lower than the NOAEL. Based on the NOAEL in cynomolgus monkeys (500 mg/kg, the highest dose tested) and using a safety factor of ten, the maximum recommended starting dose in humans was calculated to be approximately 50 mg/kg or a 3000 mg fixed dose.

Study 214367 (the COMET-ICE trial)

Study 214367 or the COMET-ICE trial is a randomised, double-blind, multicentre, placebo controlled Phases I, II and III trial of sotrovimab, a monoclonal antibody against the SARS-CoV-2 virus for the prevention of progression of mild/moderate COVID-19, who are at high risk of disease progression to severe/critical disease or death. In the trial, with interim monitoring to allow early stopping for futility, efficacy, or safety.

Participants with early COVID-19 and who were at risk for progression of disease were randomised 1:1 to receive a single, intravenous infusion of either sotrovimab or equal volume saline placebo over 1 hour. Comparisons of safety and efficacy were based on data from concurrently randomised participants.

The study comprises two phases, a lead-in phase and an expansion phase:

- The lead in phase served as the first in human assessment and included 21 participants with COVID-19 confined for 7 days to assess the safety and tolerability of sotrovimab. One participant terminated from the lead in phase early due to withdrawal of consent. The independent data monitoring committee reviewed the unblinded data from 20 participants who had completed Day 15 and recommended the study to proceed with the expansion phase to enrol additional participants across each treatment arm (1340 participants in total). Unblinded safety and efficacy data

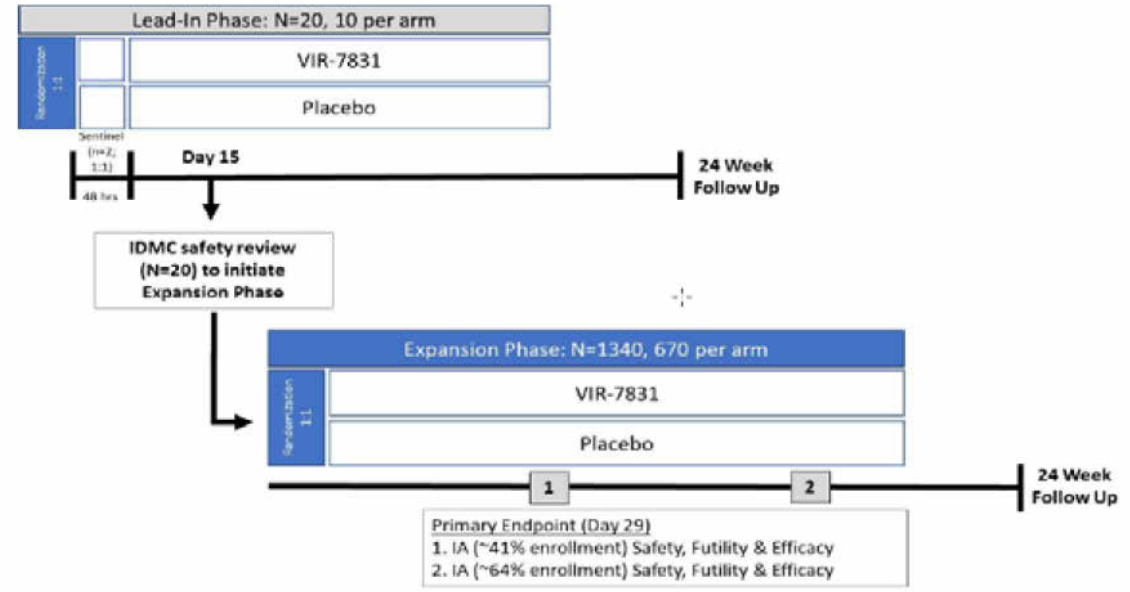
[22] EC_{90} is the concentration that leads to a 90% maximal response.

were reviewed regularly by an independent data monitoring committee throughout conduct of the study.

Study design

Figure 2, shown below, provides a summary schema and flow chart of the Study 214367/ COMET-ICE trial design.

Figure 2: Study 214367 (COMET-ICE trial) schema and flow chart of study design



N = number of planned subjects to be recruited; VIR-7831 = drug development code for sotrovimab; IDMC = independent data monitoring committee; IA = interim analysis (population).

Study 214367 (COMET-ICE trial) comprised of two phases, a lead in phase, and an expansion phase.

The lead in phase, was to recruit and randomise 20 subjects to receive either VIR-7831 (sotrovimab) or placebo) in a 1:1 ratio; that is, 10 subjects in each treatment group. All subjects underwent at 24 week follow up. At Day 15 post initiation of treatment (VIR-7831 (sotrovimab) or placebo), the independent data monitoring committee undertook a safety review of all 20 subjects, to decide on the suitability to initiate an expansion phase.

The expansion phase, involved the recruitment of 1340 subjects, randomised in a 1:1 ratio to receive either VIR-7831 (sotrovimab) or placebo; that is 670 subjects per treatment arm. All enrolled subjects received a 24 week follow up. The primary endpoint was at Day 29, and was at based on safety, futility and efficacy with 1. around 41% enrolment and 2. around 64% enrolment.

The study design was in line with FDA guidance.[23]

Primary endpoint

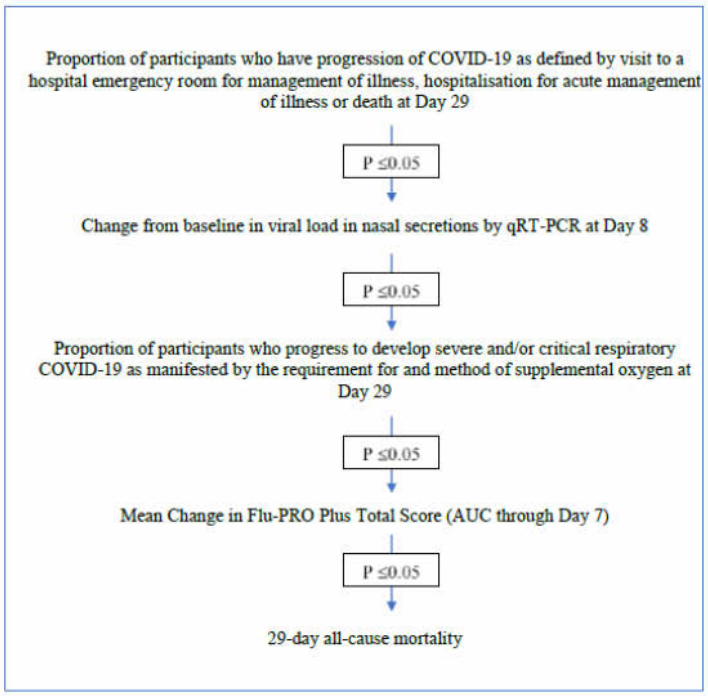
The protocol defined primary efficacy endpoint was the proportion of participants who had progression of COVID-19 through Day 29 as defined by hospitalisation > 24 hours for acute management of illness (that is, excludes hospitalisation for observation only, hospitalisation for elective surgeries and procedures, and so on) or death due to any cause. Participants in the lead in phase were included in the analysis of efficacy as defined in the protocol. The sample size determination included those from both the lead in and expansion phases accordingly. Approximately 1360 (680 per arm) participants were to be randomly assigned to study intervention.

[23] FDA 2021. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention; Guidance for Industry. Available at: https://www.fda.gov/media/137926/download

Secondary endpoints

Secondary endpoints were formally analysed only at the Day 29 analysis and were tested with alpha level of 5% (two sided). The testing of secondary endpoints was adjusted for multiplicity by using the hierarchy shown in Figure 3: Study 214367 (COMET-ICE trial) Secondary endpoints testing hierarchy below. As such, the full alpha was transferred down between each endpoint/hypothesis. All secondary endpoints in the testing hierarchy are presented along with the nominal p value of the analysis and an overall summary of progress through each stage of the testing hierarchy was provided for inferential purposes.

Figure 3: Study 214367 (COMET-ICE trial) Secondary endpoints testing hierarchy



qRT-PCR = quantitative reverse transcription polymerase chain reaction; FLU-PRO = inFLUenza patient reported outcome questionnaire; AUC = area under the concentration versus time curve.

To progress through the hierarchy of secondary endpoints, a P-value of ≤ 0.05 was necessary. The hierarchy of secondary endpoints was as follows:

1. Proportion of participants who have progression of COVID-19 as defined by visit to hospital emergency room for management of illness, hospitalisation for acute management of illness or death at Day 29.

2. Change from Baseline in viral load in nasal secretions by qRT-PCR at Day 8.

3. 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 29.

4. Mean change in Flu-Pro Plus total score (AUC through Day 7.

5. 29-day all-cause mortality

Key inclusion criteria

Key inclusion criteria were:

Participant aged 18 years or older *and* at high risk of progression of COVID-19 based on presence of one or more of the following risk factors: diabetes (requiring medication), obesity (body mass index > 30 kg/m^2 (original protocol); or > 35 kg/m^2 (as according to Amendment 1), chronic kidney disease (that is, an estimated glomerular filtration rate (eGFR) of < 60 by Modification of Diet in Renal Disease study criteria), congestive heart

failure (NYHA class II or more);[24] 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)

Or:

- Participant ≥ 55 years old, irrespective of co-morbidities. (note: enrolment was targeted to approximately 15% of participants to be > 70 years old)
- Participants who had a positive SARS-CoV-2 test result (by any validated diagnostic test, for example, via quantitative reverse transcription polymerase chain reaction, antigen-based testing on any specimen type); and
- oxygen saturation ≥ 94% on room air; and
- have COVID-19 defined by one or more of the following symptoms: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhoea, shortness of breath on exertion; and
- less than or equal to 5 days from onset of symptoms

Key exclusion criteria

Key exclusion criteria were:

- currently hospitalised or judged by the investigator as likely to require hospitalisation in the next 24 hours;
- symptoms consistent with severe COVID-19 as defined by shortness of breath at rest or respiratory distress or requiring supplemental oxygen;

  participants who, in the judgement of the investigator, are likely to die in the next 7 days;
- severely immunocompromised participants, including but not limited to cancer patients actively receiving immunosuppressive chemotherapy or immunotherapy, those with a solid organ transplant or allogeneic stem cell transplant within the last 3 months, or those having conditions requiring the use of systemic corticosteroids equivalent to ≥ 0.5 mg/kg of body weight per day of prednisone within 6 weeks of randomisation;
- previous anaphylaxis or hypersensitivity to a monoclonal antibody;
- enrolment in any investigational vaccine study within the last 180 days or any other investigational drug study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer;
- enrolment in any trial of an investigational vaccine for SARS-CoV-2;
- receipt of any vaccine within 48 hours prior to enrolment. Receipt of a SARs-CoV-2 vaccine prior to randomisation at any time point. Vaccination (including vaccination for SARS-CoV-2) will not be allowed for 4 weeks after dosing; or

[24] The **New York Heart Association** (**NYHA**) **Functional Classification** is amongst the most commonly used classification systems for heart disease. It places patients in one of four categories based on how much they are limited during physical activity. Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath). Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath). Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea. Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

- receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 monoclonal antibody within the last 3 months.

Statistical analysis plan

The primary endpoint is proportion of participants who had progression of COVID-19 as defined by hospitalisation > 24 hours or death through Day 29. It was selected prior to protocol finalisation and the first subject first visit and remained the same throughout the study.

The analysis of the primary endpoint for the interim analysis population (intention to treat population) was the same as that described for the primary endpoint for the full population (intention to treat population at Day29).

The interim analysis was performed by an independent statistical data analysis centre and was reviewed by the independent data monitoring committee (N = 583 for efficacy and N = 868 for safety) (data cut off date of 4 March 2021). As planned prospectively in the independent data monitoring committee charter, the p-values at the interim analysis were plotted against predetermined stopping boundaries. The efficacy success boundary was crossed. Therefore, the independent data monitoring committee recommended the study stop per the decisions planned prospectively in the charter. Group sequential techniques were to be used to adjust stopping boundaries to reflect the actual number of participants with available data for the primary endpoint at the time of each interim analysis. The full decision criteria for the futility due to lack of efficacy and efficacy rules along with additional information presented to the independent data monitoring committee were defined in the independent data monitoring committee charter and associated documents, as well as in the analysis plan.

Secondary endpoints were formally analysed at the Day 29 analysis and were tested with alpha level of 5% (two sided). The testing of secondary endpoints is adjusted for multiplicity by using the hierarchy, as discussed above.

Study recruitment and analysis of results

To assess safety, efficacy and futility, two interim analyses were planned:

- Interim analysis 1 at approximately 41% of participants enrolled.
- Interim analysis 2 at approximately 64% of participants enrolled.

As planned, interim analysis 1 was performed by an independent statistics data analysis centre and data was reviewed by an independent data monitoring committee (N = 583 for efficacy and N = 868 for safety) with a data cut off of 4 March 2021. The independent data monitoring committee recommended that the study met the criteria for stopping enrolment due to profound efficacy on the primary endpoint of reducing hospitalisation > 24 hours for acute management of illness or death due to any cause by Day 29 with a data cut off of 27 April 2021). The COMET-ICE trial (Study 214367) has closed for enrolment and all the randomised participants continue to be followed until their Week 24 visit follow up assessment or early withdrawal.

The interim analysis 2 will not be performed as the study met criteria for stopping early at the interim analysis 1. Results from the interim analysis 1 supported temporary authorisation applications in spring of 2021 globally. Following the independent data monitoring committee's decision to stop enrolment into the COMET-ICE trial (Study 214367) due to profound efficacy, the final participant was enrolled with an overall population of 1057 (intent to treat for Day 29 analysis: intention to treat population at Day 29).

Subsequently, the planned Day 29 analysis was conducted when data were available from all randomised participants (N = 1057). Following all participants completing the final

follow up visit at Week 24, the final safety analysis will be performed and will be reported separately.

As per the sponsor, due to the timing of the cut off date for the all cause mortality endpoint, only data up to Day 29 is reported in this submission. All cause mortality at Day 60 and Day 90 will be reported in the Week 24 analysis clinical study report. Viral load data reported in this submission includes approximately 90% of all nasopharyngeal samples through Day 29. This 90% includes visits where no viral load data will be available (for example, discontinuation, missing visits, sample not taken; < 10% of visits). Endpoint analyses results that are not currently reported in the Day 29 analysis clinical study report will either be reported in a clinical study report amendment or the Week 24 analysis clinical study report depending on timing of data availability and analysis.

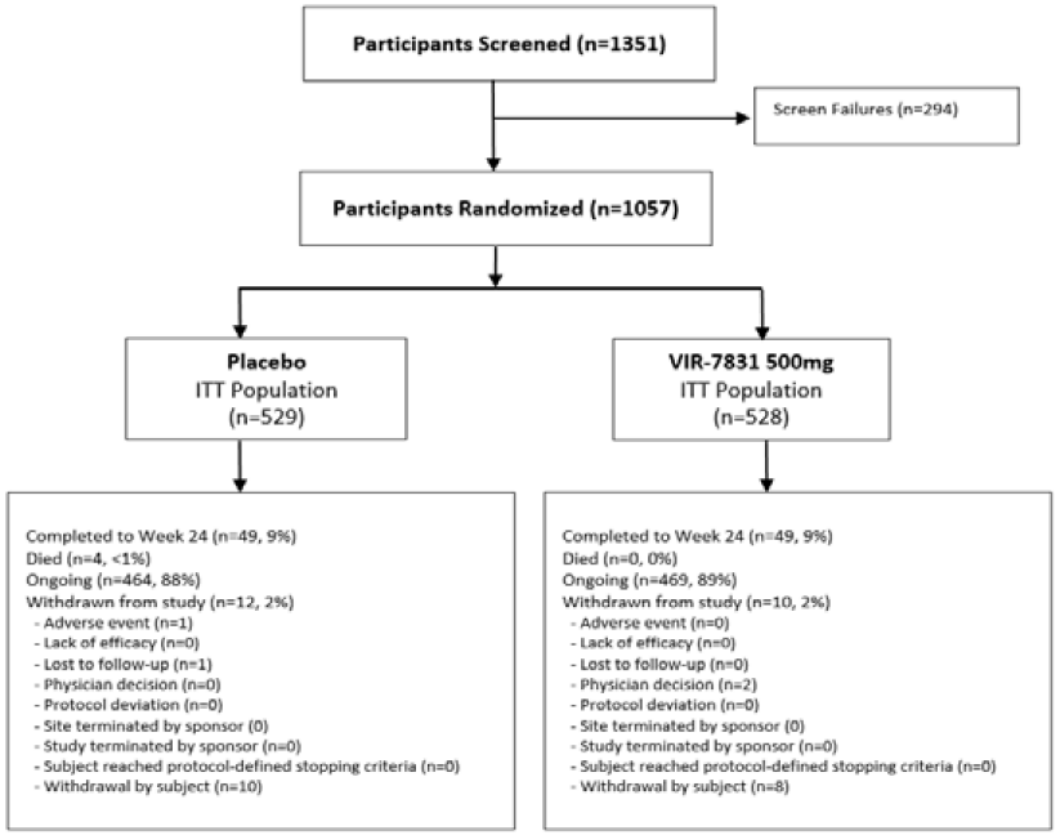
Participants were enrolled from 57 centres: 45 centres in the USA, 6 in Brazil, 3 in Spain, 2 in Canada, and 1 in Peru. The first participant was enrolled on 27 August 2020 and the last participant completed their Day 29 visit on 8 April 2021 (Day 29 Analysis). Most participants (90%) were recruited from sites in the USA.

A total of 1351 participants were screened and 294 were considered as screen failures. Overall, 1057 participants (intention to treat population at Day 29) were randomly assigned to study treatment (sotrovimab: 528; placebo: 529). A total of 1049 participants were confirmed to have received the study treatment (sotrovimab: 523; placebo: 526) and were therefore included in the full safety analysis population. Eight participants were randomised and not dosed and so were not included in the full safety analysis population.

Similar disposition was observed across both treatment arms.

Figure 4: Study 214367 (COMET-ICE trial) Participant disposition through Day 29 (intention to treat population at Day 29) shown below, provides an overview of participant disposition in the study through to Day 29.

Figure 4: Study 214367 (COMET-ICE trial) Participant disposition through Day 29 (intention to treat population at Day 29)



n = number of participants; VIR-7831 = drug development code for sotrovimab; ITT = intention to treat.

1351 participants were screened, with 294 screening failures, giving 1057 participants randomised. Of these, participants were randomised in a 1:1 ratio to receive either placebo treament (total of 529 participants) or VIR-7831 500 mg (that is, 500 mg of sotrovimab). These are included as the intent-to-treat populations.

Of the 529 randomised to placebo, 49 (9%) participants completed to Week 24; 4 parcipants (< 1%) died; 484 parcipants (88%) were ongoing involvement in the trial; and 12 partcipants (2%) withdrew from the trial. Of these withdrawals, 1 was due to adverse events, 1 was due to loss to follow-up, and 10 were due to withdrawal of consent by parctipant.

Of the 528 randomised to active treatment, 49 (9%) participants completed to Week 24; no parcipants (0%) died; 469 parcipants (89%) were ongoing involvement in the trial; and 10 partcipants (2%) withdrew from the trial. Of these withdrawals, 2 were due to physician decision and 8 were due to withdrawal of consent by parctipant.

The incidence of important protocol deviations was similar across the treatment groups; the most frequent in both groups was mis-stratification at randomisation (28% in both treatment groups). The majority of mis-stratification protocol deviations were for the duration of symptoms stratum. Duration of symptoms was determined based on the data collected in the electronic case report form, not the assigned stratum at randomisation.

Demographics and baseline characteristics

Overall, the intended population enrolled was as defined in the protocol; less than 1% had no risk factors for COVID-19 progression. Demographic and baseline characteristics were generally well balanced across the treatment groups; no remarkable differences were observed at baseline, between participants randomised to receive sotrovimab versus those randomised to placebo. Based on age and comorbidities, the COMET-ICE trial

(Study 214367) population was representative of patients who are at risk for progression to hospitalisation or death.

Of the 1057 participants, 54% were female and the median age was 53 years (range: 17 to 96 years). Further evaluation of age by predetermined age groups showed that 20% of participants were aged 65 years or older and 11% were over 70 years. While a subgroup analysis of the primary endpoint for this cohort over 70 was not statistically significant (relative risk ratio of 0.31 (95% CI: 0.07, 1.41)), this may have reflected the small number of events and does not confirm an absence of efficacy in the elderly. The point estimate was similar to what was observed in younger adults (0.18). Based on the available efficacy data, it is reasonable to include elderly subjects within the indication. At Baseline, the majority of the participants (85%) were confirmed positive for SARS-CoV-2 virus by a local reverse transcriptase-polymerase chain reaction test result, and the remainder (15%) by a positive antigen test result, with the proportions for each method similar across both treatment arms. Baseline viral load was similar across treatment arms for all baseline viral load cut-off groups. Over one-third of participants in the intention to treat population had a baseline viral load exceeding log 10^7 copies/mL, and half of participants in the intention-to-treat population had a baseline viral load exceeding log 10^6 copies/mL, consistent with previously reported data for anti-SARS-CoV-2 monoclonal antibody studies.[25]

Greater than 99% of participants in both treatment arms had at least one risk factor associated with COVID-19 progression. The four most common pre-defined risk factors or co-morbidities in both treatment groups at screening were obesity, 55 years of age or older, diabetes requiring medication, and moderate to severe asthma. The proportion of randomised participants with current medical conditions at baseline was similar across the treatment groups. Excluding the COVID-19 risk factors detailed above, the most commonly reported co-morbidities (> 10% either arm) were hypertension, hyperlipidaemia, gastroesophageal reflux disease and high cholesterol; these were well balanced between the arms.

Concomitant medications (including those commenced prior to study) were generally balanced between the treatment groups. Dexamethasone was the most commonly received steroid (sotrovimab 5%, placebo 7%). Other potentially relevant concomitant medications are summarised below in Table 2: Study 214367 (COMET-ICE trial) Potentially relevant concomitant medications

Table 2: Study 214367 (COMET-ICE trial) Potentially relevant concomitant medications

Concomitant medication; n(%)	placebo	sotrovimab
Dexamethasone	35 (7%)	27 (5%)
Ivermectin	11 (2%)	4 (< 1%)
Hydroxychloroquine*	2 (< 1%)	4 (< 1%)
Convalescent plasma*†	3 (< 1%)	2 (< 1%)
Remdesivir†	6 (1%)	1 (< 1%)
Systemic anti-infectives	76 (14%)	84 (16%)
COVID-19 vaccine∞	6 (1%)	11 (2%)

*protocol deviations; † all used in subjects who has progressed to hospitalisation; ∞ No information found in complete study report on timing on vaccination (that is whether these were breakthrough infections and/or protocol deviations). It is not stated what proportion of subjects receiving dexamethasone comprised protocol deviations due to the dose being equivalent to ≥ 0.5 mg/kg of prednisone.

Median duration of follow up was 103 days for sotrovimab and 102 days for placebo.

[25] Fajnzylber, J., Regan, J., Coxen, K. et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun 11, 5493 (2020).

Results for the primary efficacy analysis

Treatment with a single 500 mg dose of sotrovimab resulted in a statistically significant reduction in the proportion of study participants with COVID-19 progressing to > 24 hours of hospitalisation for acute management of any illness or death from any cause through Day 29 when compared with placebo (adjusted relative risk reduction: 85% (97.24% CI: 44%, 96%); p = 0.002).

Table 3: Study 214367/COMET-ICE trial Proportion of participants with progression of COVID-19 through Day 29 (hospitalisation for > 24 hours or death) (intent to treat population; interim analysis) shown below, gives the proportions of participants with progression of COVID-19 (defined as hospitalisation for more than 24 hours, or death, as the outcome) for in the intent to treat population at Day 29.

Table 3: Study 214367/COMET-ICE trial Proportion of participants with progression of COVID-19 through Day 29 (hospitalisation for > 24 hours or death) (intent to treat population; interim analysis)

	Placebo (N=292)	Sotrovimab (N=291)	Risk Ratio[a] Sotrovimab: Placebo (97.24 % CI)[b] p-value
Progression Status, n (%)			
Hospitalized >24 hours for acute management of any illness or Death due to any cause	21 (7%)	3 (1%)	0.15 (0.04, 0.56) 0.002
Hospitalized >24 hours for acute management of any illness[c]	21 (7%)	3 (1%)	
Death due any cause[c]	1 (<1%)	0	
Alive and not hospitalized	270 (92%)	284 (98%)	
Missing[d]	1 (<1%)	4 (1%)	

[a] Risk ratio adjusted for treatment, duration of symptoms (≤ 3 days versus ≥ 4 days), age (≤ 70 versus > 70 years old) and gender (female versus male) as covariates.

[b] Confidence interval level adjusted for the two planned interim analyses.

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

[d] Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 3 participants randomised to sotrovimab and 1 participant randomized to placebo withdrew consent prior to dosing and 1 participant treated with sotrovimab withdrew consent by Day 8.

Based on the difference in event rates, the estimated number needed to treat is 16 outpatients (97.24% CI:20, 35) outpatients at high risk for progression to severe COVID-19 to prevent one hospitalisation or death.

The planned Day 29 analysis (data cut off of 27 April 2021) for the primary endpoint has been conducted on the intent to treat population at Day 29 (N = 1057) analysis set; treatment with sotrovimab resulted in a statistically significant reduction in the proportion of participants with COVID-19 progressing to greater than 24 hours of hospitalisation or death through Day 29 when compared with placebo (adjusted relative risk reduction: 79% (95% CI: 50%, 91%). This level of reduction in hospitalisations or death in this final Day 29 efficacy analysis is similar to that observed in the intent to treat (interim analysis) population

Six participants met progression criteria for the primary endpoint in the sotrovimab arm. There were no deaths in the sotrovimab arm.

A summary of the primary endpoint analyses was is presented in Table 4: Study 214367 (COMET-ICE trial) Summary of primary endpoint analyses (intent to treat populations, interim analysis and Day 29) shown below.

Table 4: Study 214367 (COMET-ICE trial) Summary of primary endpoint analyses (intent to treat populations, interim analysis and 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				
Hospitalized >24 hours for acute management of illness or death, due to any cause	21 (7%)	3 (1%)	30 (6%)	6 (1 %)
Hospitalized >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 hospitalized	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	
Number needed to treat[e]	13		16	

Interim analysis 1 data cut off: 4 March 2021, Day 29 analysis data cut off: 27 April 2021

[a] One participant died at home due to CVOID-19 pneumonia without hospitalisation and one participant died in hospital due to pneumonia.

[b] For the intent to treat (ITT) interim analysis: Participants withdrawn prior to Day 29 for whom progression status in 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 the intent to treat (ITT) population at (Day 29 analysis): Participant 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 $\alpha = 2.758\%$

[e] Number of participants needed to treat in order to prevent one additional hospitalisation > 24 hours or death by Day 29.

The primary endpoint result was robust to a sensitivity analysis which analysed participants with missing data as treatment failures. Only 1% of subjects were missing data.

Results for the sensitivity analysis (missing-data as progression analysis)

Results for the primary endpoint were generally consistent with those reported in the intent to treat population (interim analysis) and intent to treat (Day 29) population when, as a sensitivity analysis, participants with missing primary endpoint data were analysed as treatment failures. The adjusted relative risk reduction was 68% (p = 0.007) and 62% (p = 0.003), respectively, in the two intention to treat (interim analysis and Day 29) analyses in the risk of COVID-19 progression to hospitalisation > 24 hours for acute management of any illness or death from any cause in the sotrovimab arm when compared with placebo through Day 29 (missing progression status = treatment failure).

Table 5: Study 214367/COMET ICE trial 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 (intention to treat population (interim analysis) and Day 29) provides a 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 (intention to treat population (interim analysis) and Day 29).

Table 5: Study 214367/COMET ICE trial 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 (intention to treat population (interim analysis) and 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 (%)				
Hospitalized >24 hours or Death, due to any cause	22 (8%)	7 (2%)	35 (7%)	13 (2%)
Hospitalized >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 hospitalized	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 data cut off: 4 March 2021

Day 29 analysis data cut off: 27 April 2021

[a] For intent to treat (ITT) (interim analysis): Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 1 placebo participant who withdrew constent 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 versus placebo), duration of symptoms (≤ 3 days versus ≥ 4 days), age ≤ 70 versus > 70 years old) and gender (female versus 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 timepoint in question so may be included in more than one category.

[b] For the intent to treat (Day 29 analysis): Participant 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 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).

Results for the secondary endpoint testing hierarchy

Hierarchical statistical testing of the key secondary endpoints indicated that the results for these endpoints are statistically significant.

Table 6: Study 214367/COMET-ICE trial Summary of secondary endpoint testing hierarchy shown below, provides a summary of the secondary endpoint testing hierarchy

Table 6: Study 214367/COMET-ICE trial 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 data cut off: 27 April 2021

[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

ITT = intent to treat; ER = emergency room; CI = confidence interval; LS = least squares; SE = standard error; AUC = area under the concentration-time curve.

Progression of COVID-19 through Day 29 as defined by visit to a hospital emergency room for management of illness or hospitalisation for acute management of illness or death due to any cause (secondary endpoint)

Treatment with a single 500 mg dose of sotrovimab resulted in a statistically significant reduction in need for hospital emergency room visits for management of illness or hospitalisation for acute management of illness (any duration) or death (any cause) through Day 29 when compared with placebo (adjusted relative risk reduction: 66% (95% CI: 37%, 81%); $p < 0.001$).

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

Table 7: Study 214367 (COMET-ICE trial) Progression of COVID-19 through Day 29 as defined by visit to a hospital emergency room for management of illness or

hospitalisation for acute management of illness or death due to any cause (secondary endpoint)

	Placebo (N=529)	Sotrovimab (500 mg IV) (N=528)
Progression Status, n (%)		
Hospitalised, ER visit or Death, due to any cause	39 (7%)	13 (2%)
Hospitalised for acute management of any illness, any duration	29 (5%)	7 (1%)
ER visit due to any cause	10 (2%)	6 (1%)
Death due to any cause	2 (<1%)	0
Alive and not hospitalised and no ER visit	485 (92%)	508 (96%)
Missing[a]	5 (<1%)	7 (1%)

Day 29 analysis data cut offL: 27 April 2021

[a] A progression status of 'missing' counts participants with a missing status in the database (if any)

Change from Baseline in viral load in nasal secretions by reverse transcriptase-polymerase chain reaction at Day 8 (secondary endpoint)

The virology population (N = 733) is a subset of the intent to treat (Day 29) analysis set, which includes participants with a central laboratory confirmed quantifiable nasopharyngeal swab at Day 1. Within the virology population, 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 = 0.007).

Progression to develop severe and/or critical respiratory COVID-19 at Days 8, 15, 22 or 29 (secondary endpoint)

Treatment with a single 500 mg dose of sotrovimab resulted in a statistically significant reduction in the risk of severe and/or critical respiratory COVID- 19 through Day 29 when compared with placebo (adjusted relative risk reduction: 74% (95% CI: 41%, 88%); p = 0.002). Specifically, no participants treated with sotrovimab required high-flow oxygen, oxygen via a non-rebreather mask, or mechanical ventilation through Day 29. Ten participants treated with placebo required oxygen support via high flow nasal cannulae, non-rebreather mask or non-invasive ventilation, and 4 participants in the placebo arm required mechanical ventilation. There were no participants in either treatment arm who required extracorporeal membrane oxygenation.

Table 8: shown below provides a summary of the proportion of participants who progress to severe and/or critical respiratory covid-19 by visit at Days 8, 15, 22, 29.

Table 8: Study 214367 (COMET-ICE trial) 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 (intent to treat population at Day 29)

	Day 8		Day 15		Day 22		Day 29	
	Placebo (N=529)	sotrovimab 500 mg (N=528)	Placebo (N=529)	sotrovimab 500 mg (N=528)	Placebo (N=529)	sotrovimab 500 mg (N=528)	Placebo (N=529)	sotrovimab 500 mg (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 [a]	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 data cut off: 27 April 2021

[a] All participants status at admission is Category 1: Room air

[b] 'Any progression' defined as either dead or Category 2, 3 or 4. Categories were informed by a combination of United States (US) Food and Drug Administration (FDA) COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (February 2021) guidance and the National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale. Excludes participants who were hospitalised and did not receive oxygen therapy. Participant could have received oxygen at home or in hospital.

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

Mean change from Baseline in FLU-PRO Plus total score (area under the curve, through Day 7) (secondary endpoint)

Among participants with available FLU-PRO;[26] Plus total scores to calculate the area under the concentration versus time curve from time zero (dosing) to Day 7 ($AUC_{0\text{-}7d}$) (by mean last observation varied forward imputation), mean decreases in total score in FLU-PRO Plus were statistically significantly greater in the sotrovimab arm than in the placebo arm at Day 7, as measured by $AUC_{0\text{-}7d}$. This is supported by statistically significant differences between the sotrovimab and placebo groups up to Day 14 and 21, as measured by the areas under the time versus concentration curves from time zero (dosing) to Days 14 and 21, respective ($AUC_{0\text{-}14d}$ and $AUC_{0\text{-}21d}$).

Table 9: Study 214367 (COMET-ICE trial) Mean change from Baseline in FLU-PRO Plus total score (area under the concencentration versus time curve, through Days 7, 14 and 21)

		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 data cut off: 27 April 2021

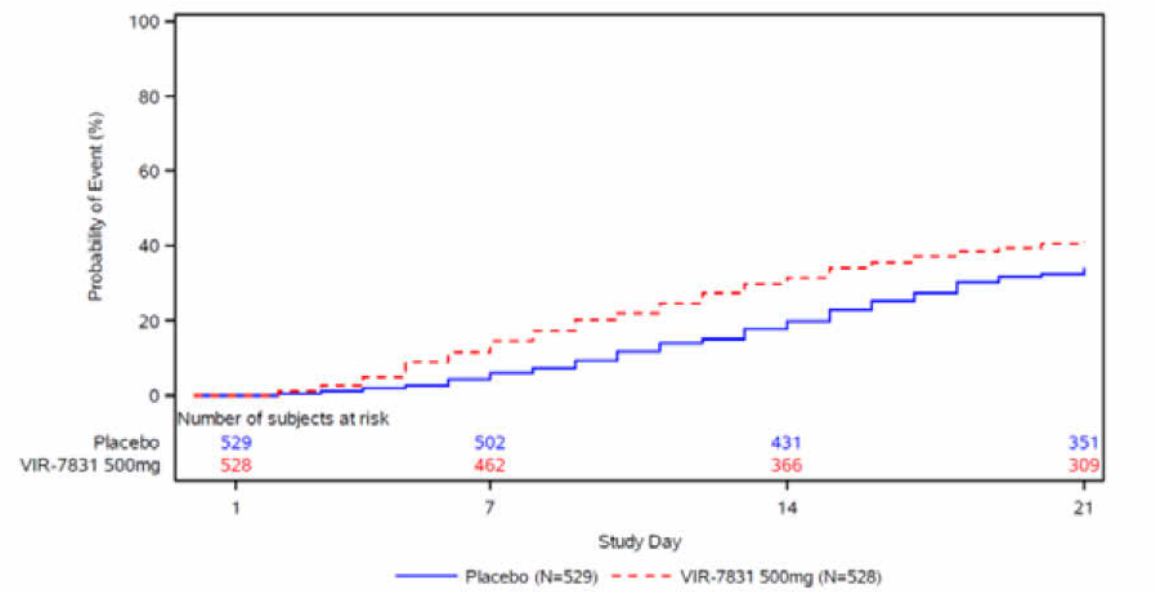
AUC = area under the concentration versus time curve; n = number of patients; CI = confidence interval.

In the intent to treat (Day 29) analysis, the probability of reaching sustained (≥ 48 hours) symptom alleviation as measured by FLU-PRO Plus was statistically significant for the sotrovimab arm (41%) compared to 34% for the placebo arm by Day 21 (log-rank test p-value = 0.002). A Kaplan-Meier plot of time to sustained symptom alleviation shows separation between sotrovimab and placebo from around Day 3 which was sustained through Day 21. It was not possible to calculate the median (50% probability of event)

[26] The inFLUenza Patient-Reported Outcome (FLU-PRO) is a patient reported outcome (questionnaire) quantifying the presence and severity of influenza or influenza-like symptoms.

time to sustained symptom alleviation for either treatment arm due to the high proportion of missing data.

Figure 5: Study 214367 (COMET-ICE trial) Kaplan-Meier plot of time to sustained symptom alleviation



Assessment of all-cause mortality at Day 29

By Day 29, 2 participants in the placebo arm had died, and no participants in the sotrovimab arm had died.

Since not all participants have had the chance to reach Day 60 or beyond at the data cut-off for the Day 29 analysis (27 April 2021), the all-cause mortality efficacy endpoint is only reported up to Day 29.

Table 10: Study 214367 (COMET-ICE trial) Summary of time to all-cause mortality at Day 29 (intent to treat population, Day 29)

Parameter	Placebo (N=529)	Sotrovimab 500 mg (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 data cut off: 27 April 2021

[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 consent at Day 16 (two participants), Day 24 (1 participant), and Day 26 (1 participant). One of the sotrovimab participant missing for the primary endopoint (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.

Of the exploratory endpoints with available results at the Day 29 analysis (total hospital length of stay, proportion of participants hospitalised due to non-respiratory complications of COVID-19, intensive care length of stay, number of ventilator days), interpretation is limited by the low numbers of hospitalisation events in subjects in the sotrovimab group. The preliminary exploratory results will not be summarised in this report for this reason.

Comparison of results in sub-populations

Overall, the results reported are generally consistent with those reported in the overall population. The overall small number of events meeting the primary endpoint (hospitalisation >24 hours or death due to any cause), and particularly the small number of events (n = 6) meeting the primary endpoint in the sotrovimab arm, make it difficult to interpret the results by subgroup. The subgroup analyses results should therefore be interpreted with caution, especially as 3 of the 6 participants (small intestinal obstruction); (non-small cell lung cancer) and (diabetic foot ulcer)) in the sotrovimab group, were hospitalised for events potentially unrelated to COVID-19.

Number of risk factors

Subgroup results were also presented according to number of risk factors with groups. A summary of primary and key secondary efficacy endpoints was presented by number of risk factors (1 or less, 2, 3 or more). The 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 risk factor subgroup. Five of six sotrovimab patients who progressed had at least 3 risk factors, of which three were hospitalised for events potentially unrelated to COVID-19.

A *post-hoc* review of all the safety narratives (Day 29 analysis) was conducted to further investigate possible relatedness to COVID-19:

Out of the 6 hospitalisations in the sotrovimab arm, 3 participants were found to have been hospitalised for events potentially unrelated to COVID-19, such as small intestinal obstruction, non-small cell lung cancer, and diabetic foot ulcer.

Thirty participants in the placebo arm met progression criteria for the primary endpoint, all of which were found to be due to events potentially related to COVID-19.

Variants of concern

The emergence of viral resistance mutants to monoclonal antibodies by SARS-CoV-2 is an exploratory endpoint of the study. An initial virology analysis was conducted based on sequencing data available as of 18 May 2021. This was reported separately from the clinical study report. Included are results from 259 participants at Baseline (sotrovimab 127; placebo 132) and 80 participants post-baseline (sotrovimab 45; placebo 35). This represents around 38% of total participants who qualify for sequence analysis (due to processing delays/resource constraints). A final virology report will be prepared later when all data are available. The presence of variants was defined as variants detected at ≥ 5% allelic fraction. Any variants in the Spike protein were present in the vast majority (> 99%) of participants with available data.

Variants in the spike protein in the epitope of sotrovimab

Variants in the epitope of sotrovimab ('epitope variants') were detected at any visit in the 19 of 275 (6.9%) participants with available data in the current analysis, including 15 (10.9%) in the sotrovimab arm and 4 (2.9%) in the placebo arm. Variants at position E340 were the most frequently observed.

Epitope variants were detected in 9 of 259 participants at Baseline (sotrovimab 5 of 127, 3.9%; placebo 4 of 132, 3.0%). No participants with epitope variants detected at Baseline met the primary clinical criteria for progression. Post-baseline epitope variants were

detected in 10 of 80 participants (10 of 45 with sotrovimab, 0 of 35 for placebo); one of these subjects met criteria for clinical progression.

Of the 17 detected unique epitope variants, 13 have been evaluated *in vitro* and most of these were neutralised by sotrovimab with fold increases in half maximal effective concentrations (EC_{50}) < 3 compared to wild type. The variants E340A and E340K resulted in significant EC_{50} shifts (> 100-fold) indicating reduced *in vitro* susceptibility to sotrovimab.

Sixty four subjects had Baseline as well as post Baseline sequencing results available for the assessment of possible treatment-emergent variants. The proportion of subjects without treatment emergent variants was similar in the placebo (6/29; 20%) and sotrovimab (6/35; 17%) arms. No subject in the placebo arm had treatment-emergent variants in the sotrovimab epitope, but these were observed in 7 subjects in the sotrovimab arm. All except for E340K had an allelic frequency of < 15%. The sponsor stated in the report that this indicated *these variants were not significantly enriched in these participants.*

Table 11: Study 214367 (COMET-ICE) Subjects with treatment-emergent variants

Treatment Arm	Participants with Paired Sequence Data, n	No TE Variants, n (%)[a]	Spike TE Variants, n (%)[a]	RBD TE Variants, n (%)[a]	Epitope TE Variants, n (%)[a]	Epitope TE Variants, (n)
Placebo	29	6 (20.1)	19 (65.5)	4 (13.8)	0 (0.0)	N/A
Sotrovimab	35	6 (17.1)	13 (37.1)	9 (27.5)	7 (20.0)	E340K (2), A344V (1), K356R (1), S359G (2), C361T (1)
Total	64	12 (18.8)	32 (50.0)	13 (20.3)	7 (10.9)	

RBD = receptor-binding domain; TE = treatment emergent; n = number of participants

[a] Percent is out of participants with paired sequence data.

Caution should be used in interpreting these observations, as the proportion of subjects with available data for this analysis was very small. It is also not certain whether the *in vitro* resistance data correlate with a reduction in clinical efficacy.

Variants of concern/interest

Available sequences were assessed for the presence of known variants of concern, variants of interest and substitutions of concern. Of those subjects with detected variants, one in each treatment group met primary endpoint criteria for progression.

Table 12: Study 214367/COMET-ICE trial Prevalent variants of concern/interest in subjects with data available as of 18 May 2021

Variant/substitution detected at any visit (n)	Sotrovimab (n = 137)	Placebo (n = 138)	Total (n = 275)
B.1.1.7 (alpha)	5	6*	11
B.1.351 (beta)	0	0	0
P.1 (gamma)	0	0	0
B.1.517.2 (delta)	0	0	0

Variant/substitution detected at any visit (n)	Sotrovimab (n = 137)	Placebo (n = 138)	Total (n = 275)
B.1.427/B.1.429 (epsilon)	5*	7	12
B.1.526 (iota)	0	0	0
B.1.617.1 (kappa)	0	0	0
N501Y substitution	1	1	2
L452R substitution	0	2	2
S477N substitution	3	4	7

*Includes one subject who met primary endpoint for progression. All other subjects experienced declines in SARS-CoV-2 viral load through Day 29.

The sponsor stated that sotrovimab has shown activity *in vitro* against all detected variants of concern in study participants (fold change in 50% effective concentration (EC_{50}) < 3 compared to wild type). Activity has also been shown *in vitro* against other SARS-CoV-2 variants, including the delta variant. The sponsor stated that shifts in EC_{50} of < 3 fold are considered to be within the variation of the assay, indicating than *in vitro* activity is retained. As per the clinical overview, the complete COMET-ICE trial virology data set report should be available towards the end of 2021.

Sequencing of subjects who met the primary endpoint for progression

Two of the 6 subjects in the sotrovimab group who progressed to hospitalisation currently have sequencing data available:

- 96 years, male; no baseline sequence available due to low viral load; epsilon variant and E340K (99.9%) detected in Day 11 sample; in hospital (not in intensive care unit) 14 days requiring nasal oxygen; recovered.
- 65 years, female; no epitope variants detected (Day 1 and 8 samples available); hospitalised 3 days for small intestinal obstruction, no oxygen required; recovered.

Safety

The primary evidence in support of the safety of sotrovimab treatment is from 1049 non-hospitalised participants with mild/moderate COVID-19 in the COMET-ICE trial/Study 214367

The available safety data at the time of this submission from the ongoing COMET-PEAK, ACTIV-3-TICO and BLAZE-4 trials are included as supporting information. BLAZE-4 trial data are being provided to also support the 30-minute infusion time. This is presented separate to the pivotal study due to differences in the studies.

Summary of studies used to characterise sotrovimab safety profile at 500 mg (IV)

Table 13: Summary of studies used to characterise sotrovimab safety profile at 500 mg (intravenous studies)

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 = 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) Part B: N=86 (IV or IM) (sotrovimab = 116)
ACTIV-3 TICO (DCO: 18 March 2021)	Additional unblinded safety summary from hospitalised patients including exposure	N=360 (sotrovimab = 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 + bamlanivimab=101)

IM = intramuscular

In the COMET-ICE trial, 1049 participants (full safety analysis population) were confirmed to have received study treatment (sotrovimab: 523; placebo: 526). Overall, median duration of follow-up was 103 days (range: 5 to 178) for sotrovimab, and the median duration of follow-up for placebo was 102 days (range: 3 to 176). Of the 1049 participants, 1037 participants were followed for >29 days (of which 98 participants have also been followed through 24 weeks).

There was no formal integrated analysis of the safety data for the clinical studies which are displayed in the form of listings, frequencies, summary statistics and graphs.

Adverse events

The overall rate of adverse events was similar in those treated with sotrovimab compared to placebo (sotrovimab: 114 (22%); placebo: 123 (23%)). Further, proportion of participants with infusion related reaction is similar in each arm. The 'hypersensitivity' Standardised MedDRA[27] Query (narrow), of Grade 1 (mild) or Grade 2 (moderate), was reported in 9 participants in the sotrovimab arm and 5 in the placebo arm.

Serious adverse events and deaths

No deaths were reported in the sotrovimab arm of the study. There were four deaths reported in the placebo arm, of which two occurred before Day 29 and 2 after Day 29. Out of these three deaths were due to pneumonia and one due to respiratory failure. Serious adverse events and Grade 3 to 4 adverse events were more common in participants treated with placebo than participants treated with sotrovimab. No serious adverse events considered related to treatment by the investigator were reported in the sotrovimab arm of the study. There were four fatal serious adverse events in the placebo arm, and two serious adverse events deemed related to study drug (placebo).

[27] MedDRA = Medical Dictionary for Regulatory Affairs.

Table 14: Adverse events overview (full safety analysis population)

	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 data cut off: 27 April 2021

AE = adverse event; SAE = serious adverse event; IRR = infusion related reaction.

[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 intravenous infusion.

[b] Infusion-related reactions (including hypersensitivity) are defined using a selection of Preferred Terms (PTs) for adverse events of special interest (AESIs), which include pyrexia, chills, dizziness, dyspnoea, pruritus, rash, infusion related reaction and only includes events that starts within 24 hours of start of study treatment.

[c] Adverse events leading to dose interruption in the sotrovimab were 2 adverse events 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 infusion, including interruption, was 1 hour 17 minutes and 1 hour 8 minutes, respectively.

[d] Infusion related reactions related to study treatment were reported in 3 participants in the placebo arms: dizziness, pruritus and rash.

Of the adverse events reported in ≥ 1% of participants in either arm, events occurred more frequently in the placebo arm (COVID-19 pneumonia, headache, nausea); the sole exception was diarrhoea, which was noted more frequently with sotrovimab (eight (2%)) sotrovimab versus (four (<1%) placebo). Of the eight participants with adverse events of diarrhoea reported in the sotrovimab arm, all had Grade 1 or Grade 2 events and the outcome of diarrhoea was reported as resolved for all at the time of Day 29 analysis data cut off.

The rate of drug related adverse events was low and similar between sotrovimab and placebo (2% for each). There were eight in the sotrovimab arm with ten drug-related adverse events, all of which were DAIDS[28] Grade 1 (seven events) or Grade 2 (three events).

[28] US NIH DAIDS = United States National Institute of Health Division of AIDs. Grade 1 indicates a mild event; Grade 2 indicates a moderate event.

Immunogenicity

Available results from approximately 75% of the participants are up to Day 29. In this study, 17 participants confirmed positive at Day 1 (Baseline) for antidrug antibodies (ADA) with no increase in titre values in subsequent time points and, therefore, are not considered to have treatment induced ADAs. Ten participants confirmed positive for anti-sotrovimab antibodies at Day 29. Four of the ten participants were positive at Baseline with no boosting in titre values at Day 29 and therefore are not considered to have treatment induced ADAs. The other six participants with positive responses are currently considered to have treatment-induced ADAs: two participants were negative at Baseline and four participants have not yet had a Baseline sample analysed. There were no apparent clinical consequences related to the presence of anti-sotrovimab antibodies.

Anaphylaxis

While no anaphylaxis events have occurred in the outpatient COMET-ICE, BLAZE-4 (Arms 7 and 8), or COMET-PEAK trials to date, one participant in the hospitalised ACTIV-3 trial, experienced anaphylaxis associated with sotrovimab. Given the serious nature of anaphylaxis and potential hypersensitivity reactions observed with sotrovimab in the hospitalised trial, it is agreed with the sponsor's inclusion of a warning statement in the Product Information (PI) to communicate this potential risk along with appropriate management, should such reactions occur.

In the COMET-ICE trial, rash or other skin reactions were not reported in the sotrovimab arm in the infusion related reactions analysis above (within 24 hours of infusion) but were reported in seven participants in the sotrovimab arm through Day 29. None of these events were Grade 3 or higher or serious. Based on the overall analysis of adverse events and serious adverse events in the COMET-ICE trial, no serious delayed hypersensitivity reactions are apparent at this time.

Antibody-dependent enhancement of disease

While there was no evidence of enhanced disease in participants treated with sotrovimab in the COMET-ICE trial, there is still a theoretical possibility of increased incidence of reinfection or enhanced disease if infected again once monoclonal antibody concentrations have waned to sub-neutralising concentrations in sotrovimab treated patients.

After a review of the adverse events across the program, hypersensitivity reactions is considered an adverse drug reaction with its frequency defined as 'Common'. Overall, the available safety data support the PI recommendation to consider slowing or stopping the infusion along with appropriate supportive care if mild to moderate hypersensitivity reactions occur.

Adverse events by system

Clinical chemistry

Grade increases in chemistry laboratory abnormalities were seen in both treatment arms. Most increases were low. The majority of the participants had no change in clinical chemistry parameters or had those parameters normalise after Baseline. Changes to outside the normal range occurred at a similar frequency between the arms.

Renal

Shifts in creatinine values to Grade 3 or 4 were balanced across the arms (4% for placebo and 5% for sotrovimab. Overall, many of the participants in both arms with Grade 3 shifts had isolated increases in creatinine values that reverted back to normal/near normal values during subsequent evaluations. In other participants, there was an isolated increase at the last available laboratory visit. There did not appear to be a signal suggesting an association between renal dysfunction and treatment with sotrovimab.

Liver chemistry

Few participants in either arm had alanine transaminase (ALT) results that were ≥ 3 the upper limited of normal (ULN), with 5 out of 511 < 1% in the placebo arm and 10 out of516 (2%) in the sotrovimab arm. No participants in either arm met Hy's Law criteria.[29] Of note, this study did not exclude participants on the basis of hepatic function. Numerically more participants in the sotrovimab arm met laboratory criteria for hepatocellular injury ((ALT/ALT ULN) / (alkaline phosphatase (ALP)/ALP ULN)) ≥ 5 and ALT ≥ 3 x ULN) (3 out of 511 (< 1%) in the placebo arm versus 6 out of516 (1%) in the sotrovimab arm).

Liver transaminase elevations have been reported commonly in the setting of COVID-19 infection.[30,31] These elevations in the sotrovimab arm were generally transient or in the setting of risk factors such as alcohol hepatitis. A single participant with a sustained rise and an ALT > 5 x ULN entered the study with elevated ALT levels. Overall, the data do not suggest a clear association between liver injury and administration of sotrovimab.

Haematology

The majority of participants had no change in haematology parameters or had those parameters normalise after Baseline. Changes to outside the normal range occurred at similar frequency between the arms.

Vital signs

There were only minor changes in the mean systolic and diastolic blood pressure, the mean pulse rate, mean respiratory rate and temperature between Baseline and Day 29. These changes were generally similar across treatment arms.

Electrocardiograms

Electrocardiogram outcomes were interpreted as abnormal but not clinically significant by the investigator in 25% of the sotrovimab treated participants at Baseline; this frequency decreased to 11% by Day 8. Overall, no clinically meaningful changes were noted with sotrovimab treatment.

Safety in special groups/situations

Adverse events by age

Adverse events and serious adverse events were assessed in the COMET-ICE trial participants who were >55, 55 to 64, 65 to 74, 75-84, and ≥ 85 years of age. COVID-19 is expected to be more severe in the elderly population. Consistent with the overall population, the overall rate of adverse events was generally similar in those treated with sotrovimab compared to placebo. Differences in adverse event rates (such as those seen in the age groups 65 to 74 and ≥ 85 years) need to be interpreted with caution given the small sample sizes.

[29] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.
[30] Marjot T, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol. 2021 May;18(5):348-364.
[31] Metawea MI, Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. Dig Liver Dis. 2021 Feb;53(2):146-152.

Table 15: Number of adverse events by participants according to age

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

Renal or hepatic impairment (Baseline alanine transaminase level and Baseline glomerular filtration rate)

The incidence of adverse events was similar between both the treatment arms for each of the renal impairment category. Overall, adverse events were more common in participants with moderate or severe renal impairment.

Hepatic function was defined based on the maximum Common Terminology Criteria for Adverse Events (CTCAE) grade for ALT at Baseline (normal = Grade 0 to 1, mildly impaired = Grade 2, moderately impaired = Grade 3, severely impaired =Grade 4). Due to the small numbers of participants with an impaired Baseline hepatic function, a meaningful comparison based on baseline hepatic function could is difficult to make.

Table 16: Number of adverse events in participants with renal or hepatic impairment (full safety analysis population 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%)

Use in pregnancy and lactation

Women who were pregnant or breastfeeding were not enrolled in COMET-ICE trial, and no participants became pregnant during the course of the study. One patient in the ACTIV-3-TICO trial was pregnant, but no data are provided. Effects on embryofetal development have not been evaluated in animal studies. Hence, there are no clinical data on human fertility, pregnancy or lactation. Human immunoglobulin G such as sotrovimab can potentially pass the placental barrier from mother to fetus.

Supporting safety data from other studies

Three clinical studies in addition to the pivotal COMET-ICE trial 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 the COMET-PEAK, ACTIV-3-TICO and BLAZE-4 trials.

The COMET PEAK trial provides only serious adverse event data (blinded). 30 participants were enrolled in Part A and no serious adverse events were reported in these participants. In Part B, 86 participants have been enrolled and six serious adverse events were

reported. The six serious adverse events occurred in four patients. None were considered related to sotrovimab by the investigator.

In the BLAZE-4 trial based on the available safety data, no serious adverse events, infusion related reactions related to study treatment, or adverse events that led to discontinuation have been reported. Follow-up is ongoing.

No serious adverse events or adverse events that led to discontinuation have been reported in BLAZE-4 trial. Five treatment-emergent adverse events (5%) were reported in the sotrovimab-bamlanivimab combination arm; two mild (Preferred Terms: eczema and paraesthesia) and three moderate (Preferred Terms: gastroenteritis, nasopharyngitis, and erectile dysfunction). Participants will continue to be followed for 24 weeks. Sotrovimab showed a favourable safety profile with infusion related reactions occurring in 1% of all participants regardless of treatment in the COMET-ICE trial and no infusion related reactions reported in the BLAZE-4 trial based on available safety data. In light of these findings, the sponsor believes the proposed 30 minutes infusion time for sotrovimab is appropriate.

In the ACTIV-3-TICO trial there was no evidence of a difference between treatment groups of a composite safety endpoint of Grade 3/4 adverse events, serious adverse events, 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 were observed in two participants, who received sotrovimab. In total, 19 participants died; 11 in the sotrovimab group and 8 in the placebo group.

One case of potentially life threatening allergic reaction (anaphylaxis) was reported following infusion of sotrovimab in the ACTIV-3-TICO trial in hospitalised patients; the patient received adrenaline (epinephrine) and the event resolved. In total, 19 participants died; 11 in the sotrovimab group and 8 in the placebo group. All deaths have been attributed to COVID-19 except two in the sotrovimab group whose Medical Dictionary for Regulatory Affairs (MedDRA) Preferred Terms were reported as 'multiple organ dysfunction syndrome' and 'lung neoplasm malignant'. In the ACTIV-3/TICO trial, 'serious' conditions including deaths that are known to occur as complications of COVID-19 were not reported as serious adverse events (unless judged to be related to the study treatment) but were designated as protocol specified exempt events and collected separately as clinical organ failure and serious infections. Serious adverse events were reported for 7 participants (3.8%) in the sotrovimab group and 9 participants (5.1%) in the placebo group. One participant in the placebo group experienced 3 serious adverse events during 2 separate clinical events.

A high proportion of serious outcomes can be expected in a population hospitalised for COVID-19. Of note these safety issues do not cause safety concerns for this application because the included population are different.

Clinical evaluator's recommendation

Based on the evaluation of the clinical data, the clinical evaluator recommends provisional approval of Xevudy (sotrovimab), subject to PI amendments.

In line with the requirements for provisional registration, it is a recommended condition of approval that completed clinical study reports for the COMET-ICE, COMET-PEAK, ACTIV-3-TICO (sotrovimab arm), COMET-TAIL, BLAZE-4 and COMET-PACE trials and the pregnancy registry data be submitted as soon as these become available.

Risk management plan

The sponsor has applied to register a new biological entity, sotrovimab (Xevudy) through the Provisional Approval Pathway.

The sponsor has submitted EU-risk management plan (RMP) version 1 (undated; data lock point: 27 April 2021) and Australian-specific annex version 1.0 (dated 2 July, data lock point: 27 April 2021) and an updated Australian-specific annex version 1.1 (dated 4 August 2021) have been evaluated. Following recommendation from the RMP evaluator, sponsor has submitted ASA version 1.2 (dated 10 August 2021). This updated ASA also refers to the date of EU-RMP version 1 as 21 June 2021.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 17: Summary of safety concerns.[32]

Table 17: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity[1]	ü	ü[2]	ü	–
Important potential risks	Antiviral resistance[1]	ü	ü[2]	–	–
Missing information	Use in pregnancy	ü	ü[2, 3]	ü	–
	Use in severely immunocompromised patients[1]	ü	ü[2]	–	–
	Use in COVID-19 vaccine breakthrough infection[1]	ü	ü[2]	ü	–
	Use in children ≥ 12 to < 18 years old	ü	ü[2, 4]	ü	–

[1] Australia specific safety concerns

[2] Monthly summary safety reports

[3] COVID-19 International Drug Pregnancy Registry (COVID-PR)

[4] COMET-PACE trial (overseas)

[32] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The sponsor has updated the ASA to include the following as Australia specific safety concerns: hypersensitivity (important identified risk), antiviral resistance (important potential risk), use in severely immunocompromised patients (missing information), and use in COVID-19 vaccine breakthrough infections (missing information).

The sponsor has agreed to include Australian patients in the COVID-19 International Drug Pregnancy Registry and submit monthly summary safety reports to the TGA. Australian patients are not to be included in the paediatric COMET-PACE trial due to the low patient number. However, findings from the study are considered applicable to Australia.

Recommendations to improve patient selection and post-infusion monitoring have been made for the Delegate to consider.

There is no new or outstanding recommendation from the RMP evaluator.

RMP evaluator recommendations regarding conditions of registration

The suggested wording is:

> *The Xevudy EU-Risk Management Plan (RMP) (version 1, undated, data lock point 27 April 2021), with Australian Specific Annex (version 1.2, dated 10 August 2021), included with submission PM-2021-01848-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the periodic safety update report (PSUR) requirement:

> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*
>
> *Additional to the submission of PSURs, expedited Xevudy monthly summary safety reports (including safety data for patients in Australia and reporting of Australia specific safety concerns) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.*

As Xevudy is a new biological entity, it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Sotrovimab (Xevudy) is to be included in the Black Triangle Scheme. The PI and CMI for Xevudy must include the black triangle symbol and mandatory accompanying text for the period of provisional registration.*

As Xevudy is being considered for a provisional registration, confirmatory trial data is recommended for the condition of registration. The following wording based on the proposed clinical study plan in the ASA version 1.2 is provided as a preliminary suggestion for the TGA Delegate to consider. The final condition of registration is to be determined by the TGA Delegate:

Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically the sponsor must conduct studies as described in the clinical study plan in version 1.1 (dated 4 August 2021) of the Australia-specific annex. The following study report(s) should be submitted to TGA:

- *Study VIR-7831-5001 (214367), (also known as COMET-ICE)*
- *Study 216912 (also known as COMET-PEAK)*
- *Study INSIGHT Protocol Number: 014/ACTIV-3-TICO (215149)*
- *Study VIR-7831-5008 (217114), (also known as COMET-TAIL)*
- *Study J2X-MC-PYAH (PYAH 05), (VIR-7831-5007), (also known as BLAZE-4)*
- *Paediatric Study COMET-PACE*

Further guidance for sponsors is available on the TGA website.

Risk-benefit analysis

Delegate's considerations

There remains an urgent need for effective therapeutics and/or preventive vaccines to reduce the burden and spread of disease. Given the ongoing high rates of COVID-19-associated hospitalisations globally, there is an urgent unmet medical need for therapeutics in the outpatient setting.

Quality and nonclinical

All outstanding quality and nonclinical issues have been resolved.

Efficacy

Sotrovimab is a Fc modified human immunoglobulin G subtype 1 monoclonal antibody that binds to a highly conserved epitope on the spike (S) protein receptor binding domain of SARS-CoV-2 with high affinity outside of the receptor-binding motif. The efficacy programme comprises one pivotal trial, the COMET-ICE trial; a Phase II/III trial at a single 500 mg IV dose.

Pharmacology and pharmacokinetics

In a small lead-in phase, the mean C_{max} was 219 μg/mL following a 1 hour IV infusion. Mean serum level on Day 29 is 37.2 μg/mL. The estimated steady-state volume of distribution was 8.1 L indicating limited distribution outside the vascular space. Sotrovimab had a mean clearance of 125 mL/day and a median half-life of 48.8 days. Partial sparse serum PK through study Day 29 from 363 participants in the expansion phase of the COMET-ICE trial was available to date. The mean serum concentration of sotrovimab on study Day 29 was 25.8 μg/mL.

In the PopPK analysis, the PK data is well described by an IV bolus two-compartment model with first-order elimination. Body weight and body mass index are covariates of sotrovimab exposure. Given the flat dosing, the magnitude of effect of body weight (and body mass index) on the sotrovimab, exposure/PK is considered clinically not meaningful. After adjusting for body weight and body mass index, age, race, ethnicity, disease severity, comorbidities, renal impairment, hepatic markers and ADA are not covariates of sotrovimab exposure.

The sponsor was asked to justify the use of first generation data in support of this application, given second generation is intended for commercial supply. The sponsor stated that the first and second generation versions of sotrovimab are expected to be clinically equivalent based on extensive *in vitro* comparability studies and emergent clinical data. A high degree of analytical and bioanalytical comparability was said to be demonstrated between first generation and second generation material. Emergent data on the second generation are available from four studies (BLAZE-4 trial, COMET-PEAK trial, COMET-TAIL trial and GSK Study No. 217653). [Information redacted]. The sponsor stated that the marginally higher peak (end of infusion) concentration and higher Day 29 second generation concentrations provide favourable clinical exposure comparability with first generation, with no dosing adjustment required for the second generation. No serious safety concerns have been identified in ongoing studies with the second generation formulation. From the totality of the preclinical and available clinical data, the sponsor considers that first and second generation materials are clinically comparable. This is considered acceptable. The nonclinical data on this has been evaluated in the nonclinical report.

In response to justify the recommendation in the PI to infuse over 30 minutes, given this was performed over one hour in the COMET-ICE trial the sponsor stated that the infusion time of sotrovimab was 60 minutes in the COMET-ICE trial and 30 minutes in the BLAZE4 trial. The recommended infusion time of 30 minutes is supported by safety data from the BLAZE-4 trial, in which no serious adverse events or infusion-related reactions were reported after a 30 minute infusion duration. The population differences between these studies would not be expected to affect rates of infusion-related reactions.

The sponsor proposes sotrovimab dosing in adolescents aged 12 years and older and weighing at least 40 kg; however, there are no clinical data available in subjects aged under 18 years. Efficacy in adolescents aged 12 years and older weighing at least 40 kg has been extrapolated from adults, using allometric scaling to account for effects of body weight on exposure. This proposal is based on an allometric scaling approach implemented in the model which accounts for effects of body weight changes associated with age on clearance and volume of distribution, and relies on the conclusion of the PopPK analysis that no dosage adjustment is required across the subject weight range of 40 kg to 160 kg. The sponsor proposes dosing adolescents based on conventional, long-established, allometric assumptions, with scaling powers for volume and clearance of 1.0 and 0.75, respectively.

In response to a request to clarify the clinical relevance of the effects of weight on exposure, the sponsor stated that the clinical significance of weight as a determinant of exposure has been mitigated by choice of a necessarily conservative dose to preserve pharmacological activity against future variants of concern. A margin for reduced potency of up to ten-fold was chosen; much greater than the exposure range expected for body weights noted in the COMET-ICE trial. The sponsor noted that subgroup analyses of the efficacy results for the COMET-ICE trial showed disparate results by body mass index and by age (event though the obese subjects had a lower median age) and concluded that weight in itself cannot be a determinant of exposure response.

To this end, the expected peak (C_{max}) and average ($AUC_{0\text{-}28d}$) exposures in 40 kg adolescents are anticipated to be (48 out of 40) 1.0 and (48 out of 40) 0.75 times higher than the 48 kg reference, that is, 120% and 115%, respectively and would be expected to afford approximately 46 fold C_{max} and 37 fold $AUC_{0\text{-}inf}$ cover compared with the preclinical 500 mg/kg no observed-adverse-effect level. Such small differences in peak and average exposure are within subject-to-subject variation, justifying the lower weight limit for the modest (22%) proportion of adolescents in the range 40 kg to 48 kg (based on simulation from NHANES data). Since adolescents are, on average, lighter than adults, sotrovimab exposure will be marginally above adults, hence the risk of under dosing adolescents with

the same 500 mg IV dose is small. Furthermore, human exposure cover is anticipated from the bodyweight range of adults treated with sotrovimab in the COMET-ICE trial (range: 49 to 183.0 kg). The sponsor therefore proposes the same dosing recommendation for adolescents (aged 12 to less than 18 years and weighing 40 kg or more) as adults. This is considered adequate and acceptable in the context of provisional registration. The planned paediatric study will provide clinical information on PKs and safety.

A single sotrovimab dose of 500 mg was selected for the study based on *in vitro* neutralisation data, *in vitro* resistance data, expected human PK extrapolated from a study in cynomolgus monkeys, and the results of the GLP standard monkey toxicology study. This is considered acceptable.

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

Clinical efficacy

Clinical efficacy of sotrovimab was demonstrated based completely from a single pivotal study, Study 214367, also known as the COMET-ICE trial. Study design, methods, conduct and analysis were satisfactory, bearing in mind that the study is ongoing and the final clinical study report is not yet available. The study design was in line with FDA guidance.[23] The majority of subjects were recruited from sites in the USA, with median age of 53 years (11% aged > 70 years) and comprising 87% White race. Most subjects (63%) were considered high risk on account of obesity, the next most frequent reason was age ≥ 55 years. 43% of subjects had 2 or more risk factors for COVID-19 progression Generally, the efficacy results are not expected to be different in the Australian population (including the Indigenous Australians); which has similar demographics and due to the high prevalence of comorbid risk factors for progression of COVID-19 observed here.

There were concerns if primary endpoint that required only hospitalisation > 24 hours or death was suboptimal because of different thresholds for hospital admission and discharge in different healthcare systems. The sponsor confirmed that patients who were hospitalised for; observation only, elective surgeries and procedures, or any other pre-planned procedures to treat underlying co-morbidities did not fulfil the criteria of acute management of illness which is required for the primary endpoint. In addition, the countries and/or sites where patients are hospitalised upon diagnosis of COVID-19 regardless of severity for observant management or for infection control purposes were excluded, to minimalise hospitalisations for reasons other than acute management. This primary endpoint was deemed optimal as it captured the totality of COVID-19 associated morbidity, while requiring illness of enough severity to merit 24 hours or more of acute hospital care.

The COMET-ICE trial met its primary objective and stopped recruitment due to profound efficacy by the independent data monitoring committee at a pre-planned interim analysis. Treatment with a single 500 mg dose of sotrovimab resulted in a statistically significant reduction in the proportion of study participants with COVID-19 progressing to > 24 hours of hospitalisation for acute management of any illness or death from any cause through Day 29 when compared with placebo in both the primary intent to treat (interim analysis) population and the intent to treat (Day 29) population. The adjusted relative risk reduction was 85% ($p = 0.002$) for the intent to treat (interim analysis) and 79% ($p < 0.001$) for the intent to treat (Day 29) populations. Risk reduction is consistent in magnitude between intent to treat (interim analysis) and intent to treat (Day 29) populations. The magnitude of the difference between sotrovimab and placebo is so large as to be clinically meaningful regardless of the specificity of the measures.

The secondary endpoints supported the primary endpoint and showed statistically significant difference between treatment arms and provide additional evidence of clinical efficacy. Most importantly, sotrovimab resulted in significant reduction in progression to

severe and/or critical respiratory COVID-19 and reductions in need for supplementary oxygen delivered by any means. Sotrovimab also resulted in significant reduction in need for hospital emergency room visits for management of illness or hospitalisation for acute management of illness (any duration) or death (any cause).

Efficacy in subjects who receive treatment later in the course of disease is not known. The COMET-ICE trial efficacy population (intent to treat population) included only one subject with symptom duration of more than 5 days. It is noteworthy that recruitment for an ongoing study of sotrovimab in hospitalised subjects with COVID-19 and symptoms ≤ 12 days in duration was ceased early for futility.

Based on the single pivotal COMET-ICE trial, sotrovimab demonstrated efficacy specifically in patients with COVID-19 not requiring supplemental oxygen. It will be appropriate to clarify this information in the indication.

Revised indication

The revised indication (proposed by TGA clinical evaluator and Delegate and accepted by the sponsor) is also for discussion at the Advisory Committee on Medicines (ACM):

> *Xevudy has provisional approval 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 progression to hospitalisation or death (see Section 5.1 Pharmacodynamic Properties, Clinical Trials).*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

The prescribers' perception of what constitutes 'at increased risk' populations may be broader than what was included in the study. 'At increased risk' is not defined in the indication. This is considered acceptable. The sponsor has provided additional subgroup analyses based on the predefined risk factors. Overall, this subgroup analysis based on the predefined risk factors underlines the challenges in identifying the population at high risk for severe COVID-19.

Variants of concern

The sponsor states sotrovimab has demonstrated activity against the current variants of concern (including delta) *in vitro*. Based on these *in vitro* data, the sponsor stated that clinical efficacy is expected. The virology data from the COMET-ICE trial 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. As per the clinical overview, the complete COMET-ICE trial virology data set report should be available towards the end of 2021.

Safety

The primary evidence for safety was provided for 523 participants in the sotrovimab treatment group (500 mg IV) of the placebo-controlled COMET-ICE trial. 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 that do not require supplemental oxygen.

The reported adverse events in the sotrovimab group (22%) was similar to the placebo group (23%). Most of these adverse events 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 adverse event (≥ 1%) consisted of COVID-19 pneumonia, headache, nausea and diarrhoea and accounts for 68 out of 237 (29%), the events occurred at low frequencies.

Serious adverse events

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

Deaths

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

Adverse drug events

No events suggestive of adverse drug events were identified during a review of renal/pulmonary/cardiac adverse events. Development of ADA is overall not considered a safety issue in a one dose treatment regimen.

Safety signals

There did not appear to be a signal suggesting an association between renal dysfunction and treatment with sotrovimab. 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.

Changes in laboratory parameters and vital signs were consistent with underlying disease and were similar in both treatment arms.

Safety in special groups

Overall, no major safety concerns for the elderly population could be identified based on the data of the clinical trials so far. However, due to the small sample size of participants > 85 years of age, no meaningful clinical conclusion can be drawn.

There are no clinical data on human fertility, pregnancy or lactation, and no participants less than 18 years old were enrolled in the clinical trials with sotrovimab.

Major adverse events of concern

Major adverse events of concern were infusion related reactions including hypersensitivity reactions. To mitigate the risk of significant infusion related reactions including hypersensitivity reactions, there is a statement in the PI:

> *Xevudy should be administered in healthcare facilities in which patients can be monitored during and for one hour after administration (see section 4.4)*.

Based on data available at present, there are no serious concerns about patients' safety; sotrovimab appears to be generally well tolerated. Long term safety data are awaited with the final study reports.

Uncertainties

While there are no currently identified safety issues that would preclude provisional registration, there are some remaining uncertainties. These are summarised below:

- The COMET-ICE trial was not powered to detect potential rare/very rare adverse drug reactions.
- Long-term safety (beyond a median follow up of 103 days) is unknown.
- There are no/limited clinical safety data in certain subgroups, in particular the following:
  - adolescents (no data);
  - pregnant/lactating women (one subject, no details available);

  - subjects with prior/concomitant COVID-19 vaccination (16 subjects with COVID-19 vaccine > 28 days after sotrovimab, none prior);
  - subjects with other concomitant vaccinations; and
  - subjects with severe hepatic or renal impairment.
- There are no data on the safety of repeat dosing with sotrovimab.
- There are limited data on the clinical relevance of anti-sotrovimab antibodies (ADAs).

Conclusions

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

Sotrovimab demonstrated statistically significant reduction in the primary endpoint of hospitalisation and death. The secondary endpoints included more COVID-19 and/or respiratory specific measures and these were all supportive of the primary result. Most importantly, sotrovimab resulted in significant reduction in progression to severe and/or critical respiratory COVID-19 and reductions in need for supplementary oxygen delivered by any means. Sotrovimab also resulted in significant reduction in need for hospital emergency room visits for management of illness or hospitalisation for acute management of illness (any duration) or death (any cause).

Based on the safety data to date, no safety concerns with IV infusion of sotrovimab were identified that would impact a favourable risk/benefit and sotrovimab was well tolerated.

Proposed action

Overall, based on the review of data on quality, safety and efficacy, the Delegate considers that the benefit-risk balance of Xevudy is favourable in the following indication:

> *Xevudy has provisional approval 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 progression to hospitalisation or death (see Section 5.1 Pharmacodynamic Properties, Clinical Trials).*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

Clinical conditions for full authorisation

The following study reports/data will have to be submitted before a definitive (full) authorisation can be considered:

- Submit the final report/clinical study report for the COMET-ICE trial with 24 weeks follow up duration when it became available.
- Submit the additional studies that are planned as part of the conditions for this provisional approval such as the COVID-International Drug Pregnancy Registry, and the paediatric COMET-PACE trial, when available.
- When available, further data relating to efficacy in immunocompromised subjects, efficacy against variants of concern, paediatric subjects, pregnant women, lactating mother, long term safety and the information relating to post-market safety and effectiveness studies should be provided to the TGA to update the PI.

Advisory Committee considerations[33]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Please comment on the revised indication (as proposed by TGA clinical evaluator and Delegate and accepted by the sponsor):

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.

The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from the ongoing and post-market assessment.

The ACM agreed that the data package is appropriate for provisional registration, however emphasised that the indication needs be targeted to those at risk of progression of COVID-19. To achieve this, the ACM agreed that the indication should link to a definition of 'increased risk' in the PI, based on the criteria in the clinical trial with further specification for some conditions, namely:

> 'Diabetes requiring medication, obesity (BMI [body mass index] > 30), chronic kidney disease (eGFR< 60 mL/min), congestive heart failure (NHYA [New York Heart Association] ≥ class 2), chronic obstructive pulmonary disease, or moderate to severe asthma (requiring inhaled steroids to control the symptoms or has been prescribed a course of oral corticosteroids in the past year), or aged 55 years and older'.

The ACM were of the view that following indication is appropriate:

> *XEVUDY has provisional approval 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 initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalisation or death (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

The ACM agreed that while the single COMET-ICE human study is pre-print and yet to be peer-reviewed, it appears to be a reasonably well-conducted study with promising interim results. The ACM emphasised that this would be the first monoclonal antibody treatment available in Australia to prevent the progression of disease in high risk patients, so is potentially a life-saving option.

[33] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM commented that the study is not powered to detect potential rare/very rare adverse drug reactions (ADRs) and that the long-term safety (beyond a median follow up of 103 days) is not known. The ACM advised that further data are needed, particularly on efficacy, safety, and pharmacokinetics in paediatric and adolescent patients, pregnancy/lactation, immunocompromised patients, hepatic and renal failure, patients who have had a COVID vaccine, and for repeat dosing.

The ACM noted there are no data currently available for the use of XEVUDY in the 12 to 18 year old age group, but agreed that pharmacokinetic data and current safety data suggest this drug may be adequately safe in this age group. The ACM were of the opinion that the overall effect size is likely to be substantially smaller in children and adolescents since this population has less progression to severe disease. The ACM advised that safety data must be gathered and provided for paediatrics (through the COMET-PACE trial and Australian data) and pregnant/breastfeeding persons (through the COVID-19 International Drug Pregnancy Registry). The ACM also advised that clinical trial and observational data should be collected to report on efficacy in this population, noting that both Study NCT04913675 (intramuscular versus intravenous Xevudy) and Study NCT04790786 (Xevudy versus other monoclonals) are currently enrolling participants aged 12 years and older.

2. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM advised that *in vivo* efficacy data needs to be collected against the delta and other variants.

The ACM agreed that additional efficacy data needs to be collected in the immunocompromised population, although they were of the view that there is no reason to believe that it would not work in this population. Ongoing data should also be collected on antibody-dependent enhancement, hypersensitivity reactions and other severe adverse drug events.

The ACM suggested an informed consent process should also be implemented for paediatric prescribing of this product, acknowledging the lack of paediatric data to date.

The ACM were of the view that use in pregnant women with comorbidities will come down to an individual risk benefit discussion between the patient and healthcare provider.

The ACM discussed risk stratification. The ACM agreed that the pivotal consideration is the comorbidities, rather than age, particularly multiple combinations of comorbidities, such as:

- diabetes requiring medication,
- obesity (BMI [body mass index] > 30),
- chronic kidney disease (eGFR < 60 mL/min),
- congestive heart failure (NHYA [New York Heart Association] ≥ class 2),[24]
- chronic obstructive pulmonary disease, or
- moderate to severe asthma (requiring inhaled steroids to control the symptoms or has been prescribed a course of oral corticosteroids in the past year).

The ACM noted that only 11% of people in the clinical studies were over the age of 70 years old, as such there is limited data to support its efficacy within this population in the absence of comorbidities.

As the therapeutic benefit of this drug is in reducing hospitalisation and ICU admission, the ACM were of the view it should be limited to patients for whom these options would be considered.

The ACM advised that Xevudy should not be used in hospitalised patients or those who require oxygen therapy due to COVID-19, and careful consideration should be given to the location of administration as there is a rare possibility of anaphylaxis. There are also no data to support to use of Xevudy in those who have had symptoms for more than 5 days.

The ACM reiterated its view that vaccination is the preferred and primary option to prevent COVID-19.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Xevudy has provisional approval 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 initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalisation or death (see Section 5.1 Pharmacodynamic properties, clinical trials).*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Xevudy (sotrovimab), 500 mg in 8 mL, concentrated injection solution for infusion, vial indicated for:

> *Xevudy has provisional approval 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 initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalisation or death (see Section 5.1 Pharmacodynamic properties, clinical trials).*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval of this indication depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*

Specific conditions of registration applying to these goods

- Risk Management Plan

  Sotrovimab (Xevudy) is to be included in the Black Triangle Scheme. The PI and CMI for Xevudy must include the black triangle symbol and mandatory accompanying text for the period of provisional registration.

  The Xevudy European Union (EU)-RMP (version 1, undated, data lock point 27 April 2021), with Australian Specific Annex (version 1.2, dated 10 August 2021), included with submission PM-2021-01848-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report

until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the submission of PSURs, expedited Xevudy monthly summary safety reports (including safety data for patients in Australia and reporting of Australia specific safety concerns) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

- Laboratory testing & compliance with Certified Product Details (CPD)
  - 1. All batches of Xevudy sotrovimab 500 mg in 8 mL concentrated injection solution for infusion, glass vial supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - 2. When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
- Clinical

  The following study reports/data will have to be submitted before a definitive authorisation can be considered:
  - Submit the final report/clinical study report for Study 'COMET-ICE' with 24 weeks follow up duration when it becomes available.
  - Submit the additional studies that are planned as part of the conditions for this provisional approval such as COVID-19 International Drug Pregnancy Registry, COMET-PACE Paediatric study, when available.
  - When available, further data relating to efficacy, safety, and pharmacokinetics in paediatric and adolescent patients, pregnancy/lactation, immunocompromised patients, hepatic and renal failure, patients who have had a COVID-19 vaccine, and for repeat dosing. Safety data must be gathered and provided for paediatrics (through the COMET-PACE trial and Australian data) and pregnant/breastfeeding persons (through the COVID-19 International Drug Pregnancy Registry). Clinical trial and observational data should be collected to report on efficacy in this population, noting that both Study NCT04913675 (intramuscular versus

intravenous Xevudy) and Study NCT04790786 (Xevudy versus other monoclonal antibodies) are currently enrolling participants aged 12 years and older. *In vivo* efficacy data needs to be collected against the delta and other variants. Ongoing data should also be collected on antibody-dependent enhancement, hypersensitivity reactions and other severe adverse drug events. Long term safety and the information relating to post-market safety and effectiveness studies should be provided to the TGA to update the Product information.

- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

  Specifically the sponsor must conduct studies as described in the clinical study plan in version 1.2 (dated 4 August 2021) of the Australia-Specific Annex. The following study report(s) should be submitted to TGA:

  - Study VIR-7831-5001 (214367), (also known as COMET-ICE)
  - Study 216912 (also known as COMET-PEAK)
  - Study INSIGHT Protocol Number: 014/ACTIV-3-TICO (215149)
  - Study VIR-7831-5008 (217114), (also known as COMET-TAIL)
  - J2X-MC-PYAH (PYAH 05), (VIR-7831-5007), (also known as BLAZE-4)
  - Paediatric study COMET-PACE

  Further guidance for sponsors is available on the TGA website.

- Quality
  - Any out of specification result of stability data must be reported to TGA immediately.

- Medicine Labels

  Unless otherwise agreed to by the Secretary following an application under section 9D of the Act, the product must only be supplied with the following labels:

  - i) the international label as follows:
    - A) carton label
    - B) vial label

  The sponsor will develop Australian-specific labels for the product, that conform with all relevant Australian labelling requirements, and will take all reasonable steps to implement such labelling before the end of the provisional registration period referred to in subsection 29(3) of the Act (being the period of 2 years starting on the day specified in the ARTG certificate of registration) (noting that, consistent with paragraph 28(5)(aaa) of the Act, changes to such matters as labels that have been agreed to as part of an evaluation under section 25 of the Act may only occur following submission under section 9D of a 'variation' application and approval by the TGA).

- Post approval commitments:
  - The sponsor will re-evaluate the specification limits of Xevudy and tighten the limits based on additional stability data and propose new limits to TGA by 17 April 2022.
  - The sponsor will complete all ongoing stability studies and report any confirmed out of specification result and proposed remediation approaches to the TGA.

- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Xevudy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au